JPRS: 3413

23 June 1960

THE CLINICAL PICTURE AND EPIDEMIOLOGY OF SOME LITTLE-KNOWN INFECTIOUS DISEASES

- USSR -

by K. G. Gapochko, N. S. Garin, and V. A. Lebedinskiy

Distributed by:

OFFICE OF TECHNICAL SERVICES
U. S. DEPARTMENT OF COMMERCE
WASHINGTON 25, D. C.
Price: $3.25

U. S. JOINT PUBLICATIONS RESEARCH SERVICE
205 EAST 42nd STREET, SUITE 300
NEW YORK 17, N. Y.

F O R E W O R D

This publication was prepared under contract by the UNITED STATES JOINT PUBLICATIONS RESEARCH SERVICE, a federal government organization established to service the translation and research needs of the various government departments.

JPRS: 3413

CSO: 3743-D

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/Following is a translation of the Russian monograph Klinika i demiologiya nekotorykh maloizvestnykj infektsiy by K. G. Gapochko, N. S. Garin, and V. A. Lebedinskiy, State Publishing House of Medical Literature, Moscow, 1957, pages 1-216./

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FOREWORD

This book contains brief reports on the nature of certain infectious diseases which seldom if ever occur in the Soviet Union and are therefore little known to the large community of physicians. The mentioned infectious diseases include psittacosis, yellow fever, the group of epidemic encephalitides, the Colorado tick fever, the hemorrhagic fever group, the American Rocky Mountain fever, the tsutsugamushi fever, and the glanders-like disease or melioidosis.

Interest in the above-listed diseases is twofold.

First of all, information on these diseases is important for an understanding of the comparative pathology and epidemiology of infectious diseases in general, especially since some of the described infections are definitely connected or even related to the infections occurring in our country. These include, for example, the group of epidemic encephalitides which have much in common with the mosquito (Japanese) encephalitis occurring in our Far East, as well as the American Rocky Mountain fever which is undoubtedly related genetically to tick-borne rickettsiosis, a disease more or less prevalent in considerable areas of Siberia and the Far East.

The infectious diseases described in this book are also of practical interest, inasmuch as under modern transportation conditions some of them may be brought into our country. This applies particularly to psittacosis, which has frequently been carried by parrots to many European countries, and to yellow fever, which has in the past also frequently spread to European ports where there is a carrier-mosquito of this viral infection, Aedes aegypti (in our country this mosquito is found along the Black Sea coast). The same may be said also of the rickettsial fever tsutsugamushi, which is endemic in our neighbor countries of East Asia.

This book includes also the group of hemorrhagic fevers occurring in our country and discovered by Soviet researchers, yet still little known to a wide circle of physicians.

The description of each infection is accompanied by brief data on the etiology, epidemiology, the clinical picture, the pathological anatomy, diagnostics, treatment, and prophylactics. Despite the brevity of the outline, the reader will be able to acquire basic information on a given group of infections. Included in the book are summary tables of the comparative characteristics and classification of the diseases designed to facilitate an understanding of the information on the large group of epidemic encephalitis and hemorrhagic fever.

The authors express their profound gratitude to Prof. Mikhail Petrovitch Chumakov, corresponding member of the Academy of Medical Sciences USSR, for his consultations and valuable advice.

P. F. Zdorovskiy, member,
Academy of Medical Sciences USSR

PSITTACOSIS (ORNITHOSIS)

Definition. Psittacosis is a viral disease of birds which is transmissible to human beings. In man the disease manifests itself as an acute generalized infection with a specific affection of the lungs.

Some researchers (Meyer, Fortner, etc.) classify as psittacosis only those infectious diseases which originate from the parrot family of birds (hence the name "psittacosis," that is, parrot disease). Very similar diseases originating from other types of wild (petrel, pigeons, etc.) and domestic (ducks, chickens, turkeys, etc.) birds are classified by these same scientists as ornithosis in view of the fact that psittacosis is different in a number of ways. First, its infective agents can be isolated; second, it is more malignant in man than ornithosis; and, finally, third, it can be transmitted from a sick person to a healthy one, which is not the case with ornithosis.

The numerous observations carried out recently, however, called for a revision of this assumption.

In a number of cases, birds of the non-parrot family were found to be the source of grave human diseases, which rules out ornithosis as a benign disease.

In the outbreak of ornithosis in the U.S. in 1952, caused by a turkey hen, four of the 63 infected persons died. During the period 1948-1954, I. I. Terskikh observed 95 cases of ornithosis in people resulting from contact with ducks and pigeons. In a number of cases this disease was very acute, although there were no fatalities. At the same time, recently published reports told of the mild forms of the disease caused by parrots.

I. I. Terskikh (1955) believes that the family of parrots, just as other birds, includes certain types and species which are carriers of highly pathogenic strains as well as those with a low pathogenicity.

An analysis of the data on ornithosis and psittacosis in recent years prompted I. I. Terskikh (1955) to state her belief that a psittacosis virus is a variation of the ornithosis virus.

In this book psittacosis and ornithosis are treated as a single disease for the purpose of simplifying the presentation.

History. Psittacosis became widely known only in 1929-1930 when 750-800 cases of the disease were registered in 12 different countries (Meyer, 1942). Psitacosis was most frequently observed in Germany and the U.S. It was established that the major source of the infection were diseased parrots brought from South America (Rubakin, 1930; Barros, 1940).

It is believed that the Brazilian jungles with their climatic, geographic, and biostructural characteristics (high humidity, abundance of animals, birds, and insects) were the first source of psittacosis and that the disease later spread to other countries between 1829 and 1930.

Eventually cases of people being infected by parrots occurred every year, and in 1935, 167 such cases were registered in Germany alone.

It was later established that in addition to South American and Australian parrots, psittacosis affects many other types of birds, both wild and domestic, which can carry the psittacosis virus and become a source of human infection. The assumption that psittacosis was caused only by the imported birds of the parrot family was thus refuted (Meyer and Eddy, 1933, 1947, 1951).

The first outbreak of psittacosis caused by birds other than parrots took place in 1938 on the Faroe Islands. The stormy petrel which is used for food by the local population was found to have been the source of the disease. The people became infected when plucking and cleaning the birds. Similar diseases were noted in Iceland in the case of people using the meat of young petrels. Cases of infection transmitted by pigeons, young chicks, ducks, and pheasants were later established in England and a number of other countries.

Cases of psittacosis have been registered in Europe in the post-war years. Thus 25 cases of the disease were observed in Western Germany (North Westphalia) in 1949-1950; 1 case of psittacosis was registered in Holland in 1947, 7 cases in 1948, and 15 in 1949 (Fortner, 1953).

Several dozen cases of people infected with psittacosis are registered in the U.S. every year, and the incidence has not diminished. The sporadic cases are sometimes accompanied by small outbreaks.

The infective agent of psittacosis was described in the 1930s by a number of researchers who had discovered tiny spherical elementary corpuscles in the reticulo-endothelial cells of the diseased birds (Levental, 1930; Lilie, 1930; Bedson and Bland, 1932; Bland and Kenty, 1935).

Methods have also been developed for cultivating the virus in chick embryos (Barnett and Roundtree, 1935; Lazarus and Meyer, 1939) and in a medium containing surviving tissue by the Cissnor method (Yanamura and Meyer, 1941).

Developed also were methods of a laboratory diagnosis of psittacosis by way of finding the virus in the sputum (Rivers and Berry, 1935) and blood of the patients, as well as by the fixation of the complement with an intracutaneous test (Barwell, 1949; Bedson, etc., 1949; I. I. Terskikh, 1954).

Before the introduction of antibiotics, the mortality rate of psittacosis was very considerable, reaching 20% and even 30%. The use of penicillin has reduced the mortality rate to a considerable extent. This disease has recently been successfully treated also with aureomycin, terramycin, and chloromycetin. The effect of the mentioned antibiotics on psittacosis is still unclear, but their effectiveness probably depends on the relation of the effective agent to the rickettsia group in the case of which these antibiotics are quite effective.

The study of psittacosis (ornithosis) in the Soviet Union has been carried out since 1948 by I. I. Terskikh, N. B. Brushlinskaya, S. I. Ratner, S. A. Reinberg, etc. In 1951-1953 these investigators

observed a large group of ornithosis patients (53 people) among the women workers of a poultry plant and a sovkoz; the infection was traced to diseased ducks and chickens.

Etiology. The infective agent of psittacosis is a filtrable virus, Rickettsiaformis psittacosis (Zhdanov, 1953), representing comparatively large coccus-shaped formations (300-450 mμ) which turn purple according to Romanovskiy-Giemsa, red according to Zdorovskiy and Machiavelli, and blue according to Kastaneda. In the smears taken of the lungs, cerebral membrane, or the abdominal cavity exudate of experimentally infected animals appear in concentrations from 1 to 7-10 μ arranged according to the stage of development in the cell protoplasm or outside the cells. In the early stages (24-44 hours) the virus is usually found outside the cells in the form of large (up to 1 μ) concentrations which, according to Romanovskiy-Giema, turn a pale violet color. Entering the cells, the virus is surrounded by a membrance, multiplies within it, and forms a colony of elementary corpuscles (Bedson and Bland, 1932). The formation of elementary corpuscles is the last phase of the psittacosis virus development; the entire cycle of this development lasts 48-72 hours. By the time they are formed, the host's affected cell dies and becomes autolytic, thereby releasing numerous elementary corpuscles which then penetrate new cells and repeat the development cycle.

The psittacosis virus can pass through Berkfelt filters, Chamberlin L_1, L_2, and L_3, but not always through Zeits filters.

By its antigenic structure the virus is close to the infective agent of an inguinal lympho-granulomatosis (Rickettsiaformis lympho-granulomatis), producing a cross reaction of complement fixation with it but differing from it only in cases of neutralization and cross resistance.

The infective agent is well cultivated on developing chicken embryos by infecting their choreo-allantoic membrane and yolk sac, as well as in media with surviving tissues or in tissue cultures.

The virus is relatively heat-resistant and it can also resist disinfectant solutions. At a 60° C temperature the viral suspension becomes completely inactive in 10 minutes. A 0.1% solution of formalin and 0.5% solution of phenol can produce a destructive effect within 24-36 hours, and a 2% solution of chloramine and potassium manganate 1:500 within 72 hours. Mention should be made of the lack of the virus' resistance to glycerin, which is the reason why the latter is never used for preserving any material containing the virus (V. M. Zhdanov, 1953).

When frozen, the virus can remain effective up to 2 years, and at a temperature of 4° C the concentrated suspensions retain their infective characteristics for 10-20 days.

When lyophil-dried and kept under low temperature, the virus remains in an active state for several months.

White mice are the most sensitive among the laboratory animals to experimental infection, and they are therefore used for isolating the virus. Introduced intranasally, into the abdominal cavity, or the cerebrum, the virus produces a disease fatal to the mice.

In the case of intraperitoneal infection the mice become ill a week after the infection. The fur of the infected animals becomes matted, the eyes are closed, and the body distended. The mice usually die 1 to 3 days later. An autopsy shows that the intestines are transparent and stretched; the liver and spleen are enlarged and covered with a white coating. A large quantity of elementary virus corpuscles is found in the coating and the cloudy exudate of the abdominal cavity, as well as in the smears of the spleen and cerebrum, when colored according to Romanovskiy-Giema and Morozov.

The washed-out elementary corpuscles can be revealed through an agglutination reaction with immune sera (I. I. Terskikh). The introduction of virus into the serum produces encephalitis in the test animals: specific pneumonia is developed by intranasal infection.

Guinea pigs and rabbits are considerably less sensitive to the psittacosis virus.

Monkeys infected intratracheally and intranasally develop pneumonia similar to the pneumonia in man.

Epidemiology. The birds are the source of the virus and psittacosis is fairly widespread among them. Of much importance in epidemiology are the virus-carrying birds in which the disease is not in any way manifested clinically.

It was originally believed that the source of psittacosis resided only in parrots (ruffle-feathered, long-tailed, and ordinary) which are found in the Australian forests and Central and South American jungles. Delivered to the stores for sale, these parrots would infect canaries, bullfinches, pigeons, and other birds with psittacosis and could also transmit the infection to man.

It was later established that spontaneous psittacosis was widespread among no less than 50 different types of wild and domestic fowl. It was discovered particularly in pigeons, petrels, fulmars, pheasants, as well as chickens, ducks, turkeys, and other birds which could themselves infect other birds and people.

Enzootic psittacosis is frequently found in poultry yards (Meyer, 1948).

The course of the disease in birds is not typical enough for a diagnosis during their lifetime. The psittacosis symptoms in parrots are refusal of food, loss of weight, diarrhea, mucous secretion from the nose, and ruffled feathers. Symptoms of pneumonia have never been observed in such cases. Parrots, particularly adult ones, can survive a light infection without even manifesting any definite symptoms of the disease.

An autopsy usually provides valuable information: the liver and spleen are found to be enlarged. The liver takes on an ochre-yellow color with yellow-gray necrotic foci.

The psittacosis virus is secreted from the organism of the diseased birds together with their excrement, saliva, and nasal mucus.

The major inlet-opening for the infection is the respiratory tract. The transmission of the disease from one bird to another and from a bird to a man occurs primarily during the inhalation of dust infected by the excrements of infected animals. Infection also occurs during the contact between healthy and diseased or dead birds or during the contact with the infected feathers, excretions, or nasal secretions of diseased birds.

Cases of laboratory infections of man point to the exceptional contagiousness of bird psittacosis, which calls for unusual care in handling infected or suspected materials.

Convincing information is now available on the possibility of transmitting the infection from a sick person to a healthy one (Luazaga, Averbakh, 1945; Eton, Beck, Pearson, 1941; Trouting and Olson, 1944).

The transmission of psittacosis from one person to another is possible through contact with the infected person during the fever phase of the disease, especially when it is accompanied by coughing. The virus secreted during the patient's coughing can produce infection primarily through the medium of air drops and air dust. The blood of patients having fever is contagious and can produce laboratory infections.

It should be emphasized that psittacosis in people is considerably less contagious than in birds and is seldom transmitted from one person to another (even in caring for patients).

A number of outbreaks affecting considerable numbers of people are described in published materials. Thus in 1892-1893 more than 50 cases of the disease connected with rabbits many of which had at the time been brought in from South America were registered in Paris; 20 cases of the disease were fatal. A large outbreak occurred in Berlin in 1898-1899 during the bird exhibition (Shubladze and Gaidamovitch, 1954).

Cases of the psittacosis disease of humans are observable everywhere (Meyer and Eddy, 1951; Lepin and Lanter, 1951). They occur, as a rule, among people having contact with birds. This disease can therefore be called an occupational disease; it affects mostly workers of poultry-dressing plants, poultry farms, pet shops, zoological gardens, etc; the disease also occurs in families which keep birds, particularly parrots or pigeons.

In the past large psittacosis epidemics usually occurred in winter. That was probably due to the lengthy contact between the people and the infected domestic poultry inside buildings. The outbreak of psittacosis on the Faroe Islands, as well as the diseases occuring among the pigeon fanciers, point to the summer and early spring as the likely seasons for such outbreaks. The data now available indicate that psittacosis occurs throughout the entire year (Meyer, 1942).

Psittacosis usually affects people of middle and advanced age. Children are also subject to the disease, but in their case the clinical picture is somewhat blurred.

There are no cases of viruses being carried for a long time by people who had gone through a clinically prominent form of psittacosis; no cases have been noted of virus carriers infecting those around them.

Pathological anatomy. Investigations of the pathological anatomy invariably reveal inflammatory changes in the lungs. The gray, gray-red, and violet inflammation carriers are indurated, forming a prominent dividing line between the normal tissue of the lung. Fresh fibrin and (petekhia) deposits are frequently seen on the pleura. The tracheal and bronchial lumens are usually free and their mucosa is unchanged. Inflammatory changes and suppurative exudation appear in the bronchi when psittacosis is aggravated by a second bacterial infection.

A microscopic investigation reveals a considerable quantity of fibrin, lymphocytes, microphages, and desquamated alviolar epitheliol cells in the alvioles. A relatively insignificant quantity of neutrophiles provides the characteristic features for psittacosis pneumonia.

The liver is moderately enlarged and full-blooded. Focal necroses are found in the parenchyma and specific elementary corpuscles in the Kupfer cells.

The spleen is usually enlarged, the number of folicles in it is small and the sinuses are filled with phagocytic cells.

There is a turbid swelling in the heart and a varying degree of parenchyma degeneration in the kidneys. Hemorrhages and capillary thrombi have been observed in adrenal patients infected with a highly pathogenic (Louisian) virus strain. Hperemia and cerebral and spinal edema are noted in many cases, as well as degenerative and proliferating changes in the endothelial vessels of the brain (Meyer, 1952).

The clinical picture. The incubation period of psittacosis lasts from 7 to 14 days, averaging 10 days; its duration sometimes extends to 25 days.

The onset of the disease is acute and sudden, but a more gradual development of the process is noted in some cases.

In the very first days of the disease the temperature rises to a subfebrile level, and later even higher (39-40°) and is accompanied by chills. In severe cases the fever remains at a high level through the second, and sometimes third, week of the disease with only slight morning remissions. The temperature usually drops gradually during the third week of the disease. In light cases the temperature returns to normal on the 7th or 8th day of the disease.

Resembling those of the grippe, the initial clinical symptoms of psittacosis are usually not sharply defined. The patient suffers from general exhaustion, increasingly severe headaches, a dry and irritating cough, and slight chills. He developes photophobia and moderate conjunctivitis; swallowing becomes painful; there is occasional vomiting. Increasing weakness and general indisposition compel the patient to remain in bed.

By the end of the first week the patient's condition becomes still further aggravated and the disease enters the critical stage, which usually lasts through the second week. By this time a typhoid condition develops, the patient becomes restless, his sleep is disturbed, and he is frequently delirious. About one fourth of the patients are affected by nosebleeds.

The pulse, as a rule, reveals a relative bradycardia. In severe cases the pulse beat becomes more rapid and weak. The arterial pressure is reduced and cyanosis developes. The critical state frequently produces a collapse.

The disease is sometimes accompanied by a normal or even increased arterial pressure (I. I. Terskikh).

Of much interest are the changes occurring in the lungs and manifesting themselves in the development of specific psittacosis pneumonia. The symptoms indicating the involvement of the lungs in the disease process can be observed in the very first days of the disease by the dry and gradual intensity of the patient's cough. But the coughing may be insignificant or lacking altogether even when the lungs are seriously affected. The usually meager sputum is at first mucus and later becomes mucus-suppurative. In rare cases it becomes bloody or rusty. To get some mucus for investigative purposes, expectorating devices or tampons have to be used. In the case of a secondary infection, however, the mucus becomes suppurative and is secreted in abundant quantities.

The frequency and depth of the respiration are not changed, but a shortness of breath (up to 60 respirations per minute) develops in fatal cases.

The physical changes of the lungs are insignificant, develop slowly, and are inconstant. One of the first pathological symptoms may be an obtusion in the lower sections of the lungs manifested under percussion.

Crepitation is revealed by the end of the first week of the disease, and later sonorous microvesicular rale.

The clinical discernment of psittacosis lung pneumonia is quite complicated and a systematic X-ray investigation of the lungs is therefore necessary. An X-ray picture taken at the end of the first week of the disease reveals the pneumonic foci which are most frequently discernible in the lower sections of the lungs.

The clinical symptoms of pneumonia begin to disappear in the third week of the disease, but the changes in the lungs as revealed by an X-ray last a longer period.

Forty-nine of the 55 ornithosis patients investigated by C. A. Reinberg, T. V. Rosenthal, and D. E. Kaplinova-Sergeyeva (1955) were found to have had pneumonia; in the case of 42 of these patients the diagnosis was confirmed by X-ray. The X-rays taken between the 5th and 8th day after the outbreak of the disease revealed focal-infiltrative changes of a lobula, segmental, or lobar type mostly of a prominent interstitial nature. The pleura was seldom involved in the pathological process.

The following gastrointestinal changes are observable in the patients during the climactic part of the disease: constipation, sometimes diarrhea, a thickened tongue covered with a gray-white coating with the imprints of the teeth along the edges. A developing meteorism results in the distention of the stomach whose palpation becomes morbid. Nausea and vomiting are fairly frequent. In most of the patients the liver and spleen become enlarged during the first days of the disease.

Various degrees of albuminuria, as well as transitory glycosuria, are frequently discerned.

The patients suffer from insomnia, apathy, depression, and sometimes delirium. Meningoencephalitis syndromes may develop in the second week of the disease.

The peripheral blood picture is characterized by a normal or somewhat reduced number of leucocytes, aneozinophilia, and a higher erythrocyte sedimentation reaction. A pronounced leucopenia occurs only in 25% of the patients. Leucocytosis occurs only at the end of the disease in the beginning of the convalescence.

A frequent complication of psittacosis is thrombophlebitis, which is the cause of pulmonary embolism.

Recuperation is slow and frequently interrupted by relapses.

Observable in addition to clinically pronounced forms of the disease are also ambulent forms lasting from one day to a week. The diagnosis in such cases is based only on the epidemiological data and the results of laboratory investigations.

Children are usually affected by mild forms of psittacosis. They complain of fatigue and a loss of appetite, and run a high temperature for a few days.

S. I. Ratner, N. B. Brushlinskaya, D. B. Mayorchuk, and R. P. Komolova (1955), who have studied the incidence of ornithosis in the USSR, divide the disease into three clinical forms:

1) the pneumonic form, manifested as an atypical pneumonia with comparatively weakly pronounced generalized toxic symptoms;

2) the typhus-life form, characterized by very priminent general toxic symptoms and comparatively rare and less prominent lung affections;

3) the grippe-like form.

These same authors describe two cases of the meningeal form of the disease.

Prognosis. Before antibiotics came into use, the psittacosis-connected mortality had fluctuated from 11 to 20%, sometimes going up to 30%. Mostly affected were people between the ages of 40 and 60.

(The figures cited in this section characterize the mortality rate during the epidemics of the severe forms of psittacosis).

After the introduction of penicillin into the medical practice, the prognosis became more favorable. Thus only 21 deaths were registered among the 228 cases investigated between 1940 and 1946. Of the 92 psittacosis patients treated with aureomycin and terramycin, two died.

According to I. I. Terskikh (1955), the treatment of psittacosis with antibiotics, begun at the proper time and properly carried out, reduced the mortality rate to 2%.

The convalescence following psittacosis is quite lengthy and the patients are incapable of work for a long time (several weeks).

Diagnosis. A diagnosis of psittacosis, particularly in the first days of the disease, is very complicated. Many cases of psittacosis apparently remain undiagnosed.

Anamnetic indications of contact with birds, particularly of the parrot family, is of essential importance for diagnosing psittacosis.

Croupous pneumonia, influenzal pneumonia and grippe, typhus abdominalis and exanthematous fever, as well as Q fever, must first be ruled out before a differential diagnosis can be made.

Croupous pneumonia differs from psittacosis by a more violent and rapid development of the disease, whereby the inflammation process in the lungs becomes clearly manifested in the very first days of the disease. The objective, particularly auscultative, data on the lungs under conditions of croupous pneumonia are considerably more definitive and undergo consistent change. Characteristic pf pneumonia also are pains in the side during breathing, coughing accompanied by a rusty sputum, unilateral cheek-hyperemia, herpes and neutrophilic leucocytosis in the pheripheral blood; finally, courpous pneumonia can be treated with sulfa drugs. As a rule, the disease is caused by a super-cooled organism.

Influenzal pneumonia may coincide with the onset and development of psittacosal tuberculosis. Influenzal pneumonia, however, is characterized by a more violet development with an expressive intoxication and more distinct percutaneous and auscultative data on the part of the lungs. In influenzal pneumonia the cough is accompanied by an abundant secretion of "mixed" sputum including mucus-suppurative, fibrinous, and sanguinolent components; finally, a more or less pronounced catarrh of of the upper respiratory tract is observable in influenzal pneumonia. Besides, the onset of the disease in a number of cases has corresponding epidemiological elements in it (grippe epidemic).

Uncomplicated grippe resembles psittacosis in its initial period, before the development of specific pneumonia. The onset of the grippe in acute form, sometimes accompanied by a catarrh of the upper respiratory tract, serves as a major premise for a differential diagnosis, in addition to the epidemiological premises.

A differential diagnosis of psittacosis with uncomplicated typhus-abdomalus and exanthematous typhus is more simple.

Spotted and enteric fever differs from psittacosis by the lack of specific changes in the lungs, which are characteristic of psittacosis, as well as by the presence of a typical rash. Spotted fever is also frequently accompanied by manifestations of meningo-encephalitis, a definite disturbance of the cardiovascular functions and a moderate leucocytosis. Enteric fever is characterized by a slower process and longer duration of the disease, as well as by pronounced changes in the small intestines.

A differential diagnosis of psittacosis and Q fever involves a number of difficulties. Both diseases are characterized by an acute development, high temperature, pronounced intoxication, severe headaches, and muscular and joint pains. Characteristic of both diseases is a relative bradycardia, and, what is particularly important, a specific affection of the lungs in the form of pneumonia develops in both cases; finally, both diseases can be successfully treated with biomycine. The peripheral blood picture also fails to provide any premises for a differential diagnosis.

In diagnosing these diseases account should be taken of the serious prognosis and high mortality rate of psittacosis, as well as of its satisfactory treatment with penicillin; Q fever cannot be treated with penicillin. The epidemiological elements of these diseases are also different: psittacosis infection is, as a rule, caused by contact with diseased birds; in the case of Q fever it is usually that contact has been made with cattle and infected dairy products used in food.

The final comfirmation of a clinical diagnosis is made by way of a laboratory diagnosis.

Laboratory diagnosis. In view of the fact that the clinical diagnosis of psittacosis in man involves great difficulties and is practically impossible in birds, a laboratory diagnosis of the disease plays a decisive part. The latter consists in isolating the elementary corpuscles of the causative virus through smears taken from the diseased animals, isolating and identifying the infective agent of the disease and the complement-fixation reaction to the blood serum of the diseased, as well as intradermal tests.

The isolation of the virus is the principal method of a laboratory diagnosis and is carried out by way of an intraperitoneal or intracerebral infection of white mice. The blood of a diseased animal taken during the first 7-8 days of the disease is used as an infective material: also the sputum, pleural fluid, and nasopharangeal

drainage in which the virus may be found from the first to the last day of the disease. During an autopsy following a psittacosis-induced death, septically removed pieces of the lungs, liver, and spleen are used as an infective material in the form of a 10% emulsion.

In the case of birds, small pieces of the liver, spleen, or exudates from the abdominal or heart cavity are used as an infective agent. Before the infection, the sputum is homogenized in a bottle of smalls, put through a centrifugal process (3,000 rpm) to remove the noxious flora, and the strained fluid is introduced into the animals. Certain researchers recommend adding a little penicillin to neutralize the noxious flora.

Chicken embryos (infected yolks) are also used for the purpose of isolating the causative agent, in addition to infecting mice.

The microscopic investigation of the sputum is of a definite value for diagnosing purposes. Elementary virus corpuscles can be found in smears colored according to Romanovskiy-Giemsa.

A complement fixation reaction with the patient's serum and an antigen prepared from a virus cultivated on a chorioallantoic membrane of a chicken embryo are used for a serological diagnosis. Complement binding antibodies appear between the 4th and 8th day of the disease.

The accumulation of antibodies during the convalescent period is particularly intensive. The antibodies also remain for a long time after recuperation.

When antibiotic therapy is energetically pursued, the emergence of antibodies is held back 20 to 40 days. The presence of complement-fixing antibodies determined by 1:16 titration in a patient with clinical symptoms of psittacosis confirms the correctness of the clinical diagnosis. The reaction dynamics is particularly important: any increase in the titer in the course of 4-5 days should be considered as a positive result.

In evaluating the complement-finding reaction results, it should be remembered that the serum of the patients suffering from inguinal lymphogranulomatosis produces a positive reaction to the psittacosal antibody. But unlike psittacosis, the antibody titer in this disease reaches its peak in the critical period and goes down in proportion to the recuperation. The blood serum of persons coming in frequent contact with a source of infection (bird owners, workers in pet shops and on poultry farms, etc.) also produces a positive reaction to complement-binding of 1:8 - 1:32 titration (Meyer, 1942). The complement-fixation reaction is used also for investigating birds suspected of psittacosis.

Virus-neutralizing antibodies accumulate in very low titers and have no diagnostic significance.

Suggested for the purpose of diagnostics is a skin test carried out with the aid of antibodies prepared from a virus culture on chicken embryos (extracted by hydrochloric acid, Barwell, 1949; Bedson, 1949).

When the reaction is positive, an infiltrate is formed at the point of the antigen introduction and a burning or itching sensation develops. The reaction results are evaluated 18, 24, 36, and 48 hours later (I. IL Terskikh).

A skin test is found to be positive after the third or fourth day of the disease, it produces the most accurate results at the end of the second week of the disease, and remains positive in convalescing patients for 2-3 and sometimes 6 months after recuperation.

Treatment. Psittacosis patients should be completely isolated during their fever stage, as well as in the period of sputum secretion. They should be hospitalized.

Specific therapy. According to American investigators, 0.5 grams of aureomycin taken every 6 hours (2 grams a day) produces good results. To avoid possible relapses, the treatment is continued for 10 days. A dose of 0.5 grams of aureomycin should be injected intramuscularly every 12 hours in patients incapable of taking it orally.

Chloromycetin (synthomycin) and terramycin, in the same dosage as aureomycin, are also quite effective.

Administered in sufficiently large doses, penicillin produces satisfactory results in the treatment of psittacosis. A hundred thousand units of penicillin should be injected intramuscularly every 3 hours for at least 10 days (Brinerd, 1954).

Regimen, diet, and symptomatic therapy. The patient must be confined to bed until the fever is over. The diet depends on the patient's general condition. He should drink 2-3 liters of liquid a day. Codeine and expectorants should be prescribed for a dry and severe cough. In case the cardiovascular functions are disrupted, camphor, caffeine, diuretin, ephedrine, or strychnine should be used. Luminal, sodium amytal (Brinerd, 1954), as well as pantopon and chloral hydrate, are recommended for insomnia and delirium furibundum.

Prophylaxis. The prophylactic measures taken against psittacosis should provide for the following:

1) strict control over the import and shipments of birds of the parrot family through a system of quarantines and laboratory investigations;

2) veterinary supervision at poultry farms, poultry plants, and pet shops;

3) the establishment of a quarantine wherever diseased birds are found. The places where the diseased birds were kept sould not be entered until they have been thoroughly disinfected with a 0.5% solution of bleaching powder, 0.5% solution of chloramine, or 3% phenol solution. The diseased birds should be killed and their carcasses placed in a 20% cresol and burned as soon as possible (before their plumage dries);

4) a detailed epidemiological and epizootological investigation of each disease for the purpose of establishing and eliminating the source of infection (the spleen of the diseased and suspected birds should be aseptically removed and sent to the laboratory for analysis);

5) the people infected with psittacosis should be isolated. The medical personnel caring for the patients should wear gauze masks, the latter to consist of several layers of gauze. All the patients' secretion, particularly the sputum, should be disinfected, and spittoons and similar containers should be filled with a 10-20% solution of bleaching powder for that purpose.

The material containing psittacosis virus should be handled and isolated in specially equipped laboratories and special precautionary measures observed.

The nasal mucus secretion of diseased birds, as well as dry excrements, are particularly dangerous. Care should be taken to see that the infective material does not get into the air. All the infective material should be handled in a box placed on a table and connected to an exhaust fan.

Rubber gloves, masks, and kerchiefs should be used in handling infectious materials and disinfected after the work. The room housing the diseased birds should be made inaccessible for insects and rodents and should be cleaned only by the spraying method. The floor of the room should be treated with a weak disinfecting solution to keep the dust down. The birds should be kept in glass jars or cages under exhaust hoods.

Specific prophylaxis. The methods of vaccination against psittacosis have not yet been completely developed. Some American researchers are in favor of the active immunization of the personnel working with psittacosis infective agents. Efforts to develop a dead psittacosis vaccine are now in progress in the U.S. Information on the degree of affectiveness of that vaccine is not available.

YELLOW FEVER

Definition. Yellow fever is an acute endemic infectious disease of viral etiology usually occurring in the tropics and transmissible by aedes mosquitoes and characterized by a high mortality rate.

History. Yellow fever has been known since the middle of the 17th century, but it has not yet been established whether its endemic source was in Africa or America.

The first yellow-fever epidemic was first reliably recorded in 1648 in Mexico (Yucatan Peninsula).

Between the 17th and 19th centuries that disease spread to the islands of the Gulf of Mexico and the Caribbean. It was observed every year in Cuba, for example, from 1649 to 1900; over 100,000 people (including 35,900 in Havana) died there of yellow fever from 1853 to 1898 alone.

From there the disease was frequently carried to the cities of North and South America along the Atlantic seaboard. Yellow fever spread also th the central areas of America with the development of navigation on the Mississippi and Amazon rivers.

It is pointed out (Reed, 1911) that about 500,000 cases of yellow fever were reigistered between 1793 and 1900 in the U.S. alone; in the cities (Baltimore, Philadelphia, and New York) the large-scale epidemics, as a rule, occurred only during the warm season of the year and died down with the beginning of the cold season.

In South America yellow fever spread to the borders of Chile and Argentina. About 23,000 people died of yellow fever in Rio de Janeiro alone between 1851 and 1885.

The etiology and the most important features of the yellow fever epidemiology were established in 1900 by Reed, who headed a commission on yellow fever created in connection with a mass outbreak of the disease among the American troops in Cuba during the Spanish-American war. The commission proved that the causative agent of yellow fever passes through the bacterial filter and is found in the patient's blood during the first days of the disease. Also established was the role of the Aedes aegypti mosquito in the transmission of the disease from one person to another.

The measures taken against the carrier mosquitoes in the first quarter of the 20th century made it possible to eradicate yellow fever in North America, on the Caribbean Islands, and in most of Central America to the north of the Panama Canal, as well as in the coastal areas of South America. The last large-scale epidemic on the coast took place in Rio de Janeiro in 1928. But sources of yellow fever still exist in the central areas of South America.

A disease quite similar to yellow fever and known in America has been recorded in West Africa since the 17th century. But its etiology remained unknown. According to some opinion expressed in

1919, the agent of the disease was the Spirochaeta icteroides discovered by Nogushi.

The next stage in the study of yellow fever was begun by American scientists under the supervision of Henry in West Africa (1925-1930). The common features between the etiology of the American yellow fever and the diseases observed in Africa were first established and it was proved that the yellow-fever agent belongs to the group of filtrable viruses (Taylor, Sellard, 1928; Bauer and Mahaffy 1930). The epidemiology of that disease was also finally established. It was found that several types of white monkeys inhabiting the jungles of West Africa and America and suffering from that disease were the reservoir of the yellow-fever virus. It was also ascertained that the virus is circulated by the bites of forest mosquitoes which can attack and infect the people inhabiting the jungles (Bauer and Mahaffy, 1930). The spread of yellow fever among people beyond the jungles had been known from Reed's work: the source of infection is an ill person and the carrier the Aedes aegypti mosquito. Further studies of yellow fever were directed primarily toward the discovery of methods of laboratory diagnosis and means of specific prophylaxis. A neutral reaction was developed and proved valuable in the study of the epidemiology and the spread of that disease. Developed also were effective live vaccines which are used successfully for the immunization of people in the endemic source areas (Taylor, 1930; Lloyd, Mailer and Ritchie, 1936; Taylor and Smith, 1937).

Yellow fever has never been observed in Asia, Australia, or East Africa. But it was frequently imported to the southern maritime areas of West Europe where a number of fairly large epidemics broke out in the past.

Cases of yellow fever have never been recorded in the USSR.

Etiology. The yellow fever agent is a filtrable virus, Viscerophilus tropicus. The elementary corpuscles of the virus are extremely small, ranging in size from 12-17 to 20-27 $m\mu$, which enables the virus to easily pass through the Zeits, Berkfelt V and N, and Chamberlin L_2 filters.

The yellow fever virus is immunologically different from other viruses; it is viscerotropic and neurotropic. Different virus strains may also have widely differing properties. The strains which are both viscerotropic and neuratropic are called pantropic. When introduced intracerebrally into mice, the pantropic virus loses its viscerotropic properties but retains and strengthens the neurotropic ones. Such strains are called neurotropic.

The virus can be well cultivated in chicken embryos (by infecting the amniotic cavity or the chorioallantoic membrane) and in tissue cultures. But the virus strains unadapted to chicken embryos are capable of causing infection only when introduced in large doses. At the same time, the virus may partially lose its virulence and pantropic

qualities when remaining for a lengthy time in chicken embryos or tissue culture.

The yellow fever virus is quite labile: it is easily inactivated by a high temperature and ordinary antiseptics. When heated to 60° C, liquid cultures become harmless in 10 minutes. But when dried, the virus has a considerably higher resistance to heat.

Disinfectant solutions rapidly kill the virus.

The best method of preserving the agent is to vacuum-dry it and keep it in sealed ampoules in a refrigerator. Another convenient method is to keep the frozen material on dry ice (the ampoules must be sealed, as the CO_2 inactivates the virus). The material containing the virus retains its effectiveness for a long time (up to 100 days) in 50% glycerin at 0° temperature. A physiologic solution rapidly inactivates the virus and cannot therefore be used for preparing a dilution. The noxious effect of sodium chloride can be eliminated by adding a 5-10% solution of normal serum to the physiologic solution (Olitskiy and Casals, 1952).

Of the experimental animals, many types of monkeys, as well as white mice, are found to be susceptible to the yellow fever virus (intracerebral infection). After the incubation period, which may vary considerably (depending on the virulence of the strain and the infection dose), the mice reveal symptoms of encephalitis and paralysis of the front and hind extremities. The monkeys infected with the pantropic strain develop typical yellow fever similar to the human disease; injected into the cerebrum, the neurotropic strain produces encephalities. Mention should be made of the fact that hedgehogs are also sensitive to intracerebral and extraneural infection.

Epidemiology. Yellow fever is an endemic disease characterized by its natural origin.

A person can be infected by the bite of a carrier mosquito. A number of cases of intralaboratory aerogenic infections have also been described (Berry and Kitchen, 1931).

Certain types of monkeys, opossums, and other wild animals inhabiting the jungles are the reservoirs of the virus. The infected animals suffer through the disease, sometimes without symptoms, and acquire immunity.

The virus is circulated among monkeys and other animals by the bite of the forest mosquito Aedes leucocelans and certain other types inhabiting the natural sources of yellow fever.

The natural foci of yellow fever are found in Central and South America and in West and Central Africa (Fig. 2).

People found within the natural sources of yellow fever are usually infected by mosquito bites.

But yellow fever is not confined to the jungles, the natural foci of that disease; spreading from there, it can cause large epidemics in inhabited points and cities.

Yellow-fever epidemics in the cities of tropical South America and West Africa are brought about by the transmission of the virus from sick to healthy persons through the medium of Aedes aegypti mosquitoes, which are widespread in those areas.

Two large yellow epidemics occurred in South America and Africa in the past 20 years.

A large epidemic occurred in the 1933-1938 period in South America. Having originated, as is believed, in the Amazon River basin, it spread southward across Brazil in the course of several years. It died down during the cold season of the year, but resumed with the onset of the summer. The first cases of the disease in the new season were frequently hundreds of kilometers away from the last cases of the previous season. A study of that epidemic proved that the haemogogus mosquitoes were in some measure responsible for spreading yellow fever.

The greatest epidemic of recent years was observed in the Sudan in 1940. Fifteen thousand cases of the disease were recorded in the course of one year, with more than 1,500 of them lethal.

The carrier of the yellow fever virus, the Aedes aegypti mosquito, belongs to the type of insects that live and develop near people's houses or even within them. The Aedes aegypti mosquitoes lay their eggs in all sorts of water containers, even very small ones (barrels, tanks, broken dishes, etc.)

In the houses these mosquitoes are usually found on the ceiling and upper parts of the wall, mostly in dark places.

This type of mosquito will bite a person in the daytime as well as at night.

The disease carrier becomes infectious after a certain period of feeding on a patient. That period varies according to the temperature: for example, at 21° C the mosquito becomes infectious in 18 days, and at 36-37° in 4-5 days; below 18 the virus can no longer develop within the organism, but its development is resumed as soon as the temperature rises again. The infected mosquitoes are capable of transmitting the virus even at a temperature of 10-15° C. The mosquitoes retain their virus-transmitting capacity throughout their lives. The possibility of the hereditary transmission of the virus is now being refuted.

(It should be pointed that the capacity of certain types of argas ticks to retain the yellow-fever virus and transmit it to their progeny under experimental conditions is referred to in available publications.)

Yellow fever cases are periodically recorded also in nonendemic areas. This may be explained by the fact that the infected mosquitoes can be moved long distances by various types of transport.

When the infection is carried to places favorable for the existence and propagation of the Aedes aegypti mosquitoes, the yellow fever may assume the proportions of a more or less large-scale outbreak. But if the area is not favorable for the life and propagation of the imported

carrier mosquitoes, the disease may break out only in individual cases, as the patients themselves cannot serve as a source of infection.

Yellow fever had been frequently imported to the southern maritime areas of Western Europe, where a number of fairly large epidemics were noted (10,000 lethal cases in the ports of Spain in 1800; 25,000 cases in Barcelona in 1821; 5,652 cases in Lisbon in 1857).

The last imports of yellow fever to Europe occurred in 1894 (Trieste) and in 1908 (France).

There have been no outbreaks of yellow fever in the Soviet Union, but the Aedes aegypti mosquitoes are found in certain areas of the Black Sea coast in the Caucasus (Sukhumi, Poti, Batumi) and the Caspian coast (Baku), which does not rule out the possibility of the disease breaking out in these areas should infected mosquitoes or patients be brought in.

The international convention concluded in 1926 provided for the introduction of quarantine methods designed to prevent the import of yellow fever (including the plague, cholera, smallpox, and spotted fever) to the countries participating in the convention. The convention signatories must report any cases of yellow fever breaking out in their territory.

The pathogenesis and pathological anatomy. The pathogenesis of yellow fever was studied in rhesus monkeys. It was proved that the virus, when introduced intracutaneously, penetrates into the regional lymph nodes where it accumulates. Several days later the virus enters the blood, infecting the liver, spleen, spine, and lymph nodes where it can be isolated after disappearing from the peripheral blood (Taylor, 1952). It can be found in human blood up to the 5th day following the onset of the disease.

The major macroscopic changes observable during autopsies are a pronounced degeneration of the liver, kidneys, and the heart, as well as symptoms of haemorrhagic diathesis and jaundice. The skin of the cadaver is of a bluish color. Jaundice is usually observed but it is seldom intensive. The liver is normal or slightly enlarged with a yellowish tint and its crosssection appears aliphatic. The kidneys are enlarged, tense and of yellow color; the cortical layer is somewhat detached from the cerebral one. Hemorrhages, most frequently localized in the mucous membrane of the pyloric section of the stomach, are observed; a changed blood is usually found in the stomach cavity.

The most typical changes in the liver can be found by a histological investigation. The liver cells are subjected to an albuminous and fatty degeneration and hyaline necrosis. The necrotized hyalinized cells are known as the Councilman corpuscles. The necrotic foci are found primarily in the central areas of the lobules, although in severe cases of necrosis they embrace almost the entire lobules. The histological changes resemble the picture characteristic of acute dystrophy (acute yellow atrophy of the liver). In the course of recovery the parenchymatous cells are regenerated and the liver's structure is almost completely restored without any residual symptoms of cirrhosis.

The changes in the kidneys can be very grave; they are manifested in the albuminous and fatty degeneration of the calaniculi which is most pronounced in their coiled part.

The spleen is usually hyperemic. Degeneration and necrosis is observed in the Malpighian corpuscles. Similar changes are found also in the lymph nodes.

Degeneration occurs also in the heart muscle; the capillary endothelium is subjected to destructive changes. The mucous pyloric part of the stomach and, to a lesser extent, the intermediary part of the small intestine are the scene of numerous small-scale hemorrhages. Small perivascular hemorrhages covering vitally important centers are observed in the cerebrum.

The symptoms of yellow fever are almost fully explained by the above-described pathological changes. A serious affection of the liver brings about symptoms of hemorrhagic diathesis and jaundice; the albuminuria is conditioned by the changes in the kidneys; lymphopenia is caused by the affection of the lymphoid tissue of the spleen and the lymph nodes; the bleeding syndromes are aggravated by the destruction of the capillaries (Taylor, 1952).

The clinical picture. The incubation period of yellow fever is usually 3 to 6 days, occasionally lasting 10-13 days (Lowe and Fairly, 1931).

The temperature curve is "saddle-shaped" in appearance. At the onset of the disease, the temperature rises very rapidly (to 39-40°), stays at that level to the 3rd or 4th day and then drops again. The normal temperature period lasts from several hours to 2 days and alternates with rising temperature, which usually lasts 3-4 days.

The disease is usually divided into the following three periods: the initial fever period (the period of active hyperemia and infection), the temperature-falling period (feebleness), and the reaction period (the period of venous stasis and the period of intoxication).

The initial fever period lasts an average of 3 days and is characterized by the presence of virusemia, high temperature, hyperemia of the face and visible mucosae, pronounced intoxication, severe headache, nausea, and vomiting.

Prodromal symptoms are usually lacking. The disease comes on suddenly, so that the patient can frequently determine accurately the time the first symptoms appeared. It begins with a rapidly increasing headache and giddiness. On the first and second day the temperature rises to 39-40° and is accompanied by shivering. The muscles and bones begin to ache; food and mucus vomiting and nausea are observed. Small children often become convulsive. An examination of the patient reveals a reddening of the face, neck, and upper part of the chest. The conjunctive are sharply inhibited, the lips are swollen and the tongue is bright red. The skin is dry and hot. The patient is stimulated, irritable, and active; his sleep is disrupted. He has a full and frequent

pulse; in the first 2-3 days of the disease it is in keeping with the temperature, reaching 100 and even 120 beats per minute. The arterial pressure is normal or even slightly high. On the 2nd day of the disease the general condition of the patient usually remains unchanged. On the 3rd and last day of the initial period the patient's condition becomes worse, frequently revealing symptoms which attain their full development only in the third period of the disease. Jaundice may be discovered as the subicterus of the sclera. The symptoms of hemorrhagic diathesis (nose and gum-bleeding), observable from the very outset of the disease, become more pronounced, and blood-vomiting ("black vomiting") resembling coffee grounds or tar-like stool is sometimes noted. The emergence of relative bradycardia and albuminuria is quite characteristic; leucopenia is in the process of developing. All these symptoms are more clearly pronounced in grave diseases and can be lacking in mild forms of the disease.

The temperature-falling period begins between the 3rd and the 5th day of the disease and lasts from several hours to 2 days. The temperature drops to normal (subfebrile, subnormal) figures and the patient suddenly feels better. The headaches and muscle aches lessen and even disappear. The nausea and vomiting stop and the patient can easily fall asleep.

It should be borne in mind that the temperature-falling period may be lacking and the initial period in such cases is followed by the reaction period. In mild forms of the disease, the temperature-falling period may end in recuperation. In most patients with a pronounced form of the disease the temperature-falling period is followed by a reaction.

Characteristic of the reaction period is the lack of virusemia, high temperature, and pronounced intoxication symptoms, as well as the development of jaundice, bleeding (blood vomiting, bloody stool), albuminuria, and bradycardia.

Although the patient's temperature is usually lower than in the initial period, his condition becomes worse.

Vomiting becomes more frequent and blood is brought up due to the bleeding in the stomach (as well as nose and gum bleeding). Blood vomiting which turns black under the effect of gastric juices (black vomiting), is one of the most characteristic and grave symptoms of yellow fever. The nosebleeds may be quite profuse. A tar-like bloody stool, an indication of gastric or intestinal bleeding, is frequently observed. Symptoms of bleeding are clearly shown on skin and mucosa lesions.

The patient's appearance undergoes a change. The active hyperemia of the outer skin changes to a venous stasis. The swelling on the face disappears and the color changes to a bluish hue. The gums become soft and begin to bleed; hemorrhages appear on the visible mucosa.

The developing jaundice is also one of the most important symptoms of the disease. "But despite the name 'yellow fever,' jaundice is not always a distinctive symptom of the disease even in lethal cases" (Kerr, 1951). It develops gradually as a rule and may range in intensity from subicterus sclera to an intensive general jaundice, which, however, is seldom observed.

The relative brandycardia observable during the reaction period becomes still more pronounced in the course of 2-3 days and frequently changes to an absolute bradycardia (the pulse frequency under high temperature may drop to 40 beats per minute). The pulse is usually weak and an extra systole is observed. The development of tachycardia in this period is a bad prognostic indication.

The heart tone is muffled and murmurs can be heard at the top. An electro-cardiogram reveals various changes arising in the myocardium; but electro-cardiogram changes typical only of this disease have not been found. Chagas and Freitas believe that the progressive changes of the S-T interval are of prognostic significance. Electrocardiographic investigations reveal that the heart may be involved in the process from the very beginning of the disease. This is the reason for the serious disruptions even in mild forms of the disease. In other cases the heart may be practically uneffected (Berry and Kitchen, 1931).

The arterial pressure as a rule drops in the second and third period of yellow fever. Severe cases may result in an arterial collapse.

No substantial changes are noted in the lungs.

The liver is enlarged, not usually compact, and painful during palpation. In severe cases of the disease, the changes occurring in the liver are brought about by the development of a seriously disrupted metabolism. In the case of monkeys, the terminal stage of yellow fever reveals that the deamination is disrupted by a developing hypoglycemia (Vakhman and Morrel, 1930). An enlarged spleen is observed in a considerable number of the sick animals. The bilirubin in the blood is, as a rule, increased.

The changes in the kidneys are quite substantial. Albuminuria, which is seldom manifested before the third day of the disease, is one of the characteristic symptoms. In a classical case, the development of severe albuminuria is swift; in a 12-hour it may increase from insignificant albumin traces in the urine to such a high content that the urine clots in the test tube when tested for albumin. Its normal content is 3-5 grams per liter of urine but it often goes up to 20 grams. Albuminuria may last several days and then disappear as fast as it appeared. In mild and very mild cases the urine may be found to contain only traces of albumin. It has been established that there is a direct relationship between the gravity of the disease and the quantity of albumin in the urine.

Another kidney symptom in cases of yellow fever is oliguria, which develops in the third period of the disease. In serious cases it may change to anuria, which, however, is seldom observed.

The daily quantity of urine may fluctuate from normal in mild cases, to very insignificant amounts (30 ml in case of anuria) in the last stages of a severe disease. The relative quantity of urine increases under conditions of oliguria and albuminuria. Quite characteristic is its acid reaction. In all forms of the disease, except the gravest, the daily secretion of urea increases. The amount of urine decreases during

convalescence. Biliary pigments are found in the urine during the recuperation period, and the urine occasionally takes on a green color.

Leucopenia, neutropenia, and lymphopenia, which develop from the first day of the disease and reach their maximum on the 6th and 7th day, are important diagnostic symptoms. The number of leucocytes drops to 1,500-2,500 per mm^3. A moderately pronounced leucocytosis is observed during the recuperation period. Around the 10th day of the disease the number of leucocytes returns to the normal level and then exceeds it. No substantial changes are noted in the picture of the red blood cells. Available data indicate an accelerated erythrocyte-sedimentation reaction, as well as a slower coagulability of the blood.

Investigations of the cerebrospinal fluid reveal increased fluid pressure, a positive non Nonne-Appelt reaction, as well as an increased content of albumin and chlorides (770-850 mg %).

In serious fulminant infections a coma of hepatic or uremic origin frequently sets in 2-3 days before death.

Shortly before death the patient's mind becomes dulled; patients are delirious and highly stimulated; wild and uncontrollable excitement serves as one of the yellow fever symptoms. The immediate reason for such phenomena apparently are the small perivascular hemorrhages in the cerebrum, especially in its brain stem (Stevenson, 1939). The above disturbances are accompanied by a quiet premortal delirium; some of the patients retain their mental faculties.

The reaction period usually last 3-4 days and in rare cases up to 2 weeks.

The convalescent period is, as a rule, lengthy and ends in full recovery. Asthenia, occasionally quite substantial, usually lasts no more than a week after the temperature drop.

Complications. Complications in yellow fever are, as a rule, rare. The most frequent complication is parotitis phlegmonosa, usually unilateral, occasioned by the penetration of a common infection from the oral cavity. Pneumonia complicates the course of the disease but does not occur frequently. A serious complication in yellow fever is myocarditis, which may be observed during the recuperation period. Lethal cases caused by myocarditis have been recorded among patients who were prematurely discharged from the hospital (Kirk, 1941).

The clinical forms of yellow fever. The following forms of yellow fever are determined by their relative gravity: 1) very mild, 2) mild, 3) average, 4) malignant, and 5) fulminant (Kerr, 1951).

1) The very mild form is characterized by fever and headaches lasting 1-2 days. It is diagnosed only by laboratory methods.

2) The mild form is accompanied by fever and a headache which are more clearly pronounced. It is also followed by nausea, nosebleeds, relative bradycardia, light albuminuria, and a subicteric feature of the sclera and skin. The disease lasts 2-3 days and ends in recovery.

The reaction period is usually absent. A clinical diagnosis is possible only when epidemiological prerequisites are available; it can be confirmed by laboratory investigation.

The mild and very mild forms of the yellow fever are recorded most frequently in the endemic sources among the children of the local population.

3) Yellow fever of average gravity can be clinically diagnosed on the basis of a pronounced fever, relative bradycardia, severe headache and in pains in the loins as well as nausea, vomiting, distinct jaundice, and albuminuria. "Black vomiting" and hemorrhages of the internal organs may be observable. The disease is always accompanied by a reaction period. The fever lasts from 5 to 7 days.

4) Malignant yellow fever, whether fatal or not, produces all the classic symptoms.

5) Fulminant yellow fever is an extremely acute and grave form of the disease ending in death on the 3rd or 4th day. All the classic symptoms are frequently present.

Children are usually subject to the light forms of yellow fever.

Prognosis. The average mortality produced by yellow fever is 5-10%, increasing to 20-25% in cases of severe epidemics. The higher mortality figures occasionally recorded show that the mild forms of the disease had not been properly diagnosed or taken into account. In certain epidemics the mortality is reduced to 1-2%.

After the establishment of the diagnosis at the onset of the disease, a further prognosis should be made with great care. The patients seldom die during the initial period of the fever. If the disease is fulminant, death may occur on the 4th day. A pronounced temperature reaction, its rapid development, as well as an early developing albuminuria, produce an adverse prognostic effect.

In making a prognosis the subjective improvement during the temperature drop should not be taken into account for 2 days, but if this is not followed by a reaction period it may be assumed that the patient has entered his recovery period.

The diseases revealing the development of a pronounced reaction period may be classified as of average and malignant forms. Half of the patients affected by these forms of the disease usually die. The most serious symptoms of the reaction period from a prognostic point of view are oliguria, restlessness, delirium, and coma. A frequent pulsebeat (100-120 beats per minute) and pronounced albuminuria and hiccups are also unfavorable from a prognostic point of view. There is a relationship between the degree of jaundice and the gravity of the disease, but patients with an intensive jaundice frequently do recover.

An abundant diuresis and a clear mind are favorable symptoms.

Death occurs most frequently between the 5th and 9th day of the disease. It occurs very seldom after the 10th day of uncomplicated yellow fever. The cases of death occurring in later periods are

probably due to the strain on a damaged myocardium.

Diagnosis. A differential diagnosis should be made of yellow fever with acute dystrophy (acute yellow atrophy) of the liver, ictero-hemorrhagic leptospirosis, Bodkins disease (epidemic hepatitus), malaria, hemorrhagic fever, and, particularly, dengue fever.

An acute or subacute dystrophy of the liver may represent a complication of both acute and chronic liver diseases; it occurs most frequently in infectious and toxic jaundice. Acute liver dystrophy is distinguishable from yellow jaundice by the following symptoms: the lack of typical fever, a progressive reduction of the liver, clearly pronounced neuro-cerebral symptoms (drowsiness, violent delirium, convulsions of certain groups of muscles, pathological reflexes, and loss of consciousness), a highly intensive jaundice with a very high content of bilirubin in the blood (up to 30 mg %), tachycardia and the lack of a pronounced albuminuria and an increasing content of amino-acids in the urine.

A differential diagnosis of yellow fever and ictero-hemorrhagic leptospirosis (Vasilev-Weil disease) is quite complicated. Both diseases are characterized by an acute onset, distinct general toxic phenomena, diphasic fever, jaundice, symptoms of hemorrhagic diathesis, albuminuria, a painful course, and high mortality. The distinctive symptoms of ictero-hemorrhagic leptospirosis are herpes, typical muscle pains, especially in the sural muscles, a pronounced tachycardia, and a characteristic blood picture (anemia, distinct neutrophylic leucocytosis with a bascillus-nuclear change, and an accelerated erythrocyte sedimentation reaction).

Ictero-hemorrhagic leptospirosis, unlike yellow fever, is widespread everywhere; rats are the reservoir of the disease and the infection occurs through the alimentary canal.

In addition to its peculiar epidemiology, Bodkin's disease (epidemic hepatitis) differs from yellow fever by the lack of a characteristic temperature curve (or complete lack of fever), mild intoxication symptoms, the lack of symptoms of hemorrhagic diathesis and albuminuria, as well as a longer though comparatively milder course.

Malaria, which is widespread in endemic yellow fever areas and has a number of common epidemiological features, differs by the intermittent nature of the temperature and the cyclical development of the disease, as well as by the absence of a distinct jaundice and hemorrhagic diathesis and albuminuria symptoms.

A differential diagnosis of yellow fever with hemorrhagic fever is not difficult. In addition to substantial differences in the epidemiology (various virus reservoirs, various carriers, etc.), hemorrhagic fever is known for the absence of jaundice or a characteristic double-peaked temperature curve, as well as for the presence of a unique rose-colored and petechial rash on the skin. Typical of the Omsk hemorrhagic fever also is a frequent affection of the lungs in the form of specific pneumonia, while a serious affection of the kidneys is peculiar to hemorrhagic nephrosonephritis.

A differential diagnosis of yellow fever with dengue fever is particularly difficult. The diagnosis is complicated by the similar areas affected in both diseases and by the similarity in the epidemiology (the same carrier mosquito, Aedes aegypti).

A clinical picture of dengue fever is sometimes so similar to that of mild forms of yellow fever that the two diseases can be told apart only with the aid of immunological reactions.

The course of dengue fever is considerably milder and mortality is practically absent; albuminuria is usually lacking and jaundice is very rarely observed. A morbilliform rash, characteristic of dengue fever, is important differential-diagnostic symptom.

Laboratory diagnosis. The following three methods are most often used for a laboratory confirmation of a diagnosis: 1) the isolation of the virus; 2) the discovery of virus-neutralizing antibodies in the patient's blood; 3) a pathohistological investigation of the liver in fatal cases.

Intracerebral-injection of white mice with the blood of sick mice taken before the 5th day of the disease is used for the purpose of isolating the virus. After the incubation period the infected animals develop a lethal encephalitis. The isolated virus should be identified, as the encephalitis in mice has no specific symptoms of yellow fever. The simplest method of identification is a neutral reaction with immune serum. The reaction is applied also to the white mice. A histological investigation should be made of the liver, spleen, and kidneys of the dead animals. The possibility of identifying the virus does not necessarily prove the absence of yellow fever.

The virus-neutralizing antibodies in the serum of the patient are found with the aid of a neutral reaction, which produces positive results in the second week of the disease and may be used for retroactive diagnosis.

The complement-fixing reaction is not widely used in view of its insufficient sensitivity.

A post-mortum diagnosis of yellow fever through the histological investigation of the liver plays a very important part in the countries where that disease is endemic. Samples taken of the liver are fixed in formalin, then placed in paraffin and dyed with a hematoxylin eosin. The diagnosis is based on the discovery of typical affections.

Treatment. There are no effective methods of treating yellow fever. No specific treatment has been developed. The use of all the known antibiotics has not been successful.

The patient must have complete rest and good care. Washing the body systematically with cool water and cold applications to the head and stomach are recommended. The oral cavity should be cleaned daily. Syringes should be used to prevent constipation and meteorism.

A proper diet is very important. The patient should be given much liquid daily. If nausea and vomiting prevent the patient from taking the

liquid orally, it should be introduced parenterally. The introduction of alkaline solutions into the organism is recommended to prevent the development of acidosis; fruit juices are very helpful. A starvation diet con taining practically no albumins or fats and including a limit quantity of hydrocarbons was used till the very last day of the yellow fever treatment. At present, however, it is found necessary to include albumin-rich products in the diet (Kerr, 1951). The most acceptable diet is milk, easily assimilable hydrocarbons and meat bouillon.

A glucose-insullin therapy combined with the introduction of vitamins C (ascorbic acid) and K into the organism should be used against intoxication and acidosis, as well as the developing hypoglycemia.

Sucking on ice may be helpful during vomiting. If this does not help, bromides and narcotics should be prescribed. Pyramidon or phenacetin should be resorted to in case of chills, high temperature, and severe headaches.

Camphor, caffeine, or ephredine should be used for maintaining the functions of the cardiovascular system. Blood transfusion and plasma are recommended in case of a collapse.

Prophylaxis. The prophylactic measures against yellow fever in the areas affected by the disease are designed to fight the mosquitoes and immunize the population.

All types of transportation facilities (air, sea, river, motor, and railroad) should be thoroughly treated with DDT and hexachlorine with a view to preventing the import of infected mosquitoes from affected areas.

The fight against the mosquitoes is designed to: 1) destroy the existing breeding places, 2) exterminate the larvae, and 3) exterminate the flying mosquitoes.

The possibility of cleaning all the water reservoirs of all the larvae may considerably reduce the necessity for special meliorative operations. The larvae can be destroyed by treating the water reservoirs with oil, kerosene, mazut, Paris green, and other powdered poisons, as well as DDT and hexachlorine. Large swampy areas can be treated by spraying them with insecticides from planes. The fight against flying mosquitoes takes on particular importance in the cities and inhabited points located in the affected areas. This can be accomplished by treating the residential and other buildings with DDT and hexachlorine. Two grams of the active substance should be used per 1 m^2 of area. The people should wear anti-mosquito nets and apply insect repellants to the exposed areas of the body and clothes (dimethylphtalate, dibutylphtalate, etc.)

The large-scale anti-mosquito measures carried out in America made it possible to eradicate a number of endemic sources and considerably reduce the incidence of yellow fever. In Africa the prophylactic measures were less intensive and consistent and the result is that the African continent is still the largest source of yellow fever.

Active specific prophylaxis consists in vaccination with live vaccines.

The vaccines are now prepared from 2 attenuated strains, the French neurotropic and the American 17-D strain. The French neurotropic strain was developed by way of lengthy intracerebral passages of the virus in white mice, and as a result it lost its pathogenicity for monkeys. That strain was used by the French to vaccinate the people against yellow fever in West and Central Africa. The vaccine is produced in the form of a dried brain of an infected mouse. The French researchers used the skin vaccination method by applying a vaccine suspension in gum Arabic to the scarred skin. The suspension is prepared just before it is used. Following an accumulation of antibodies, this vaccine becomes more immunogenic than the vaccine prepared from the 17-D strain, but it is also more reactive. The number of post-vaccination reactions is about 15%. Experimental data led some researchers to the conclusion that the French strain is not sufficiently harmless for man.

By experimenting on tissue cultures, the American researchers have developed a completely safe 17-D strain which is now widely used for vaccination purposes. The 17-D vaccine strain is prepared from infected chicken embryos and kept dry in a refrigerator. Before using, it is dissolved in a proper amount of a physiologic solution and 0.5 ml is injected under the skin. The vaccine made of this strain is not highly reactive, but on the 7th day after the vaccination approximately 5% of the subjects reveal exhaustion, headaches, and muscle pains, as well as a slight temperature reaction. This condition usually lasts not more than 2 days. Mention should be made of serious complications in the form of encephalitis occuring after the use of a certain batch of vaccines. The vaccinated subjects become immune 7-9 days after vaccination.

That the use of vaccines against yellow fever is highly effective is indicated by available data. The mass-vaccination carried out until now has produced quite satisfactory results.

In the absence of carrier mosquitoes, yellow fever patients are not dangerous for the surrounding people. In the first 6-7 days of the fever the patient should be confined to a room inaccessible to mosquitoes (net-covered windows, gauze bedcurtains, etc.).

THE EPIDEMIC ENCEPHALITIS GROUP

A large number of epidemic encephalitides is now known. Almost all of them are natural-focal and communicable diseases. Each type of encephalitis is native to its own climatic and geographical zone, depending on the natural favorable conditions for virus circulation.

For example, the tick-borne vernal encephalitis occurs in the taiga districts of the Far East and certain other areas of the Soviet Union. The Japanese mosquito encephalitis is prevalent in Japan, Korea, and certain areas of the Soviet maritime province.

There are also a number of different types of encephalitides which do not occurr in the Soviet Union but have many common clinical and epidemiological features with the encephalitides recorded in our country.

It should be pointed out that there is undoubtedly a genetic relationship between the agents of the Japanese encephalitis, the American St. Louis encephalitis, and the West Nile encephalitis; this is confirmed by both the immunological proximity of the viruses as well as by their common features of adaptation and circulation in nature.

Despite the fact that a number of the above-described encephalitis forms do not occur in the USSR, some of the carriers of that disease are widespread in our country. In this connection, the study of the epidemiological, clinical, and prophylactic characteristics of the epidemic encephalitis which does not occur in the USSR should be of some interest (Figure 4).

This chapter contains a brief description of the following forms of encephalitis which are of epidemiological importance; the American St. Louis encephalitis, the American Eastern equine encephalitis, the American Western equine encephalitis, the Venezuelan equine encephalitis, the Australian encephalitis, the Scothh Sheep encephalitis, and West Nile encephalitis.

The American St. Louis Encephalitis

Definition. St. Louis encephalitis is an acute viral epidemic disease occurring in the central and western areas of the U.S. The causative agent of the disease is carried by mosquitoes.

History. In the summer of 1932 a wide encephalitis epidemic broke out in Paris, Illinois. The first cases of the disease were diagnosed as Economo-type encephalitis and no further serious study was made.

A similar epidemic broke out the following summer in St. Louis and Kansas City, Missouri, and their suburbs. One thousand one hundred and thirty cases of the disease were recorded in St. Louis alone. A study of that form of the epidemic showed that the disease was a type of encephalitis and was named the American St. Louis encephalitis.

Sporadic outbreaks of that disease were noted in California, Ohio, Indiana, and New York in 1934. A recurrent outbreak of encephalitis in St. Louis was recorded in 1937.

The agent of the disease was isolated by Mukenfus, Armstrong, and McCordock, (1933) in monkeys, as well as by Webster and Feitam (1933) in mice.

Etiology. The agent is a filterable virus of the Neurophylus americanus type. The virus passes through the Berkefeld N, V, W, and Zeits filters. Its size is 20-30mμ. There is an antigenic relationship between the agent of the St. Louis encephalitis and those of the Japanese encephalitis (Neurophylus japonicus) and the West Nile encephalitis (Neurophylus nili).

The St. Louis encephalitis agent is less stable in the outside medium than the viruses of the other encephalitis and it dies comparatively rapidly under room temperature; it lasts a considerably longer time in the cold. When kept in glycerin on ice, the virus remains active for more than 2 months; and when vacuum-dried and kept in sealed ampoules in cold temperature, more than 17 months.

The virus can be destroyed in 30 minutes when heated to 56°, in 50 days in a 1% phenol solution, and in 10-11 hours by a 0.1% formalin solution at room temperature. The virus can be preserved in suspensions by adding a glycerophosphate buffer, temperature 4°, pH = 3.4-8.8 (Daffy, 1946).

The virus of the St. Louis encephalitis is pathogenic for many animals: cattle, horses, rabbits, hamsters, mice, as well as domestic fowl (ducks, chicks, and pigeons). Many animals, especially birds, frequently develop an asymptomatic infection in the course of which the virus is constantly revealed in the blood. Of the laboratory animals, white mice and monkeys are susceptible to it. Rabbits and guinea pigs were found to be invulnerable to the infection. In white mice the disease can be induced only by intracerebral or intransal infection; the subcutaneous, intravenous, or intraperitoneal injection of the virus does not, as a rule, produce the disease.

White mice reveal the first symptoms of the disease after 3 or 4 days of the incubation period following the intracerebral or intranasal infection: ataxia, matted wool, and spasms. Convulsions, paralysis, and prostrations appear a little later, and the animals die one to 5 days after the outbreak of the disease. The virus is isolated from the spleen blood and the tissue of the central nervous system (Peck and Sabin, 1947).

A pathohistological investigation around the brain vessels reveals an accumulation of round cells and the destruction of nerve cells, which is particularly pronounced in the horn of Ammon zone. Similar changes are found also in the spinal cord.

Monkeys are considerably less susceptible to the virus of the St. Louis encephalitis than white mice. The disease can be induced in them only by an intracerebral injection of the virus. The incubation

period lasts from 8 to 14 days; this is followed by a gradually rising temperature, a disrupted coordination of movement, and a tremor and paresis of the limbs; after that, as a rule, comes recovery. It is very difficult to isolate the virus in monkeys. Only when the animals are killed during the critical stage of the disease is it possible to isolate the virus from the cerebral tissue.

A pathohistological investigation of the monkeys reveals a degeneration and necrosis of the nerve cells in the brain, as well as a prevascular and focal infiltration.

The virus of the St. Louis encephalitis is cultivated by the usual methods. Twelve to 16-day old chidken embryos are used for producing the virus. After 3-4 days the virus multiplies in sufficient quantities to produce a diffuse infiltration with necrotic foci on the chorioallantoic membrane. The virus develops will also on tissue cultures. The medium used for that purpose consists of a crushed chicken or mouse embryo brain, a rabbit serum, and a Tirode solution (Harrison and Moore, 1936).

The serological investigations of the virus carried out in 1933-1935 by Webster, Feite, Cox, and Clowe showed that the antigenic structure of the virus of the St. Louis encephalitis is different from the agents of the other viral encephalites which have a similar clinical picture and epidemiology.

Epidemiology: The incidence of the St. Louis encephalitis is noted primarily in the western and central states of the U.S. (Illinois, Missouri, Kansas, California, Texas, Arizona, Indiana, New Mexico, and Washington). The disease has not been recorded outside of those states.

The reservoirs of the virus in nature has not been completely established. It is assumed that birds and various small rodents are the principal reservoirs. Investigations have shown that certain domestic fowl in the endemic areas contain antibodies of the St. Louis virus. For example, in the Yakima River valley (Washington), where St. Louis encephalitis cases were periodically registered during the period of 1939-1942, specific antibodies were found in 48% of the domestic fowl (Bang and Reeves, 1942). It was also established that after being bitten by infected mosquitoes and ticks, the birds reveal a virusemia for a long time and an accumulation of specific neutralizing and complement-fixing antibodies.

Specific antibodies for the virus have been found also in horses and certain other animals.

The virus carriers are the Culex tarsalis and pipiens mosquitoes and apparently certain other types of mosquitoes and possibly also gamasidae-type ticks.

It has been established under laboratory conditions that certain types of mosquitoes (Culex pipiens, Culex tarsalis, Culex coronator, Aedes luteralis, Aedes taeniarhynchus, Aedes vexans, Aedes nigro maculis) can be experimentally infected with the St. Louis encephalitis virus,

whereupon they acquire the capacity of transmitting it birds and animals.

The spontaneous infection with the virus under natural conditions has so far been discovered only in the Culex tarsalis mosquitoes (Hammond, 1942). The seasonal activity of the Culex tarsalis and Culex pipiens mosquitoes coincides with the outbreak of the disease among people. The possibility of transmitting virus to experimental animals by Dermacentor variabilis ticks has also been established (Blatner and Hayes, 1942).

In 1944, Smith, Blatner, and Hayes isolated the virus from the Dermanyssus gallinae hermesiti ticks collected from chickens in St. Louis during the interepidemic period. The ticks passed the St. Louis virus on to their progeny.

The circulation pattern of the virus in nature is apparently complicated. The formation of antral foci is possible in addition to the natural foci (Zhdanov, 1953).

A person is usually infected by a mosquito bite, but the disease may be transmitted also by ticks.

The incidence of the American St. Louis encephalitis is strictly seasonal. Thus in the Paris, Illinois, epidemic of 1932, most of the cases occurred in the month of August. The 1933 epidemic in St. Louis and Kansas City was also definitely seasonal in nature; 88.5% of all the cases occurred in August and September. The outbreak of the St. Louis encephalitis in 1937 also took place in the summer-fall season and the largest number of cases also occurred in August.

The disease affects primarily the people in the city suburbs and rural areas. Thus in 1933 there were 69 cases recorded for the 100,000 population of St. Louis and 212 cases for the 100,000 suburban population.

The largest number of cases always occurred in the areas of large water bodies (lakes and rivers) which are favorable for mosquito breeding.

All age groups were affected by the epidemic. The highest incidence was noted among young children and people over 45. In one adult population the incidence was higher among men.

The clinical picture. The incubation period lasts from 4 days to 3 weeks. Prodromal symptoms occasionally occur at the end of the incubation period: the patients complain of exhaustion, headaches, stomach aches, and muscle pains; occasionally conjunctivities is revealed. The disease takes an acute course. The body temperature rises to 40-41°, and is followed by vertigo, ataxia, a rigidity of the occipital muscles, and the loenig symptom. The patient's mind is disordered, there is a tremor in the limbs, and paralysis develops.

The disease is particularly serious in the case of young children, frequently ending in death within 2 to 4 days. In 10 to 40% of the infected children under 6 months, the nervous system is, as a rule, seriously affected to the extent of producing an epilectic condition. The disease is somewhat less serious in the case of older children; but even in such cases it is frequently acute and fulminant and ends in death.

Neutrophylic leucocytosis (10,000-14,000 leucocytesper 1 m^3) is usually found in the patient's blood.

The cerebrospinal fluid is clean and oozes out under slight pressure; it contains pleocytosis (from 300 cells and up) with lymphocytes and monocytes predominating. The quantity of albumin is somewhat increased and the sugar content does not exceed the norm.

In serious cases recuperation may take several months, but in milder cases the disease may be over in several weeks. The recovery is, as a rule, complete in adults and older children. About 5% of the former patients, however, retain residual symptoms in the form of weakness, tremors, and mental debility. The mortality rate fluctuates according to the age of the patients, from 5 to 30%.

Pathological anatomy. A macroscopic test reveals a hyperemia of the vessels and a petechial hemmorrhage in the membranes and tissues of the brain; the fluid is transparent.

A microscopic investigation reveals a hyperemia of the meningeal and cerebral vessels, hemorrhages, and perivascular infiltrates consisting primarily of lymphocytes with an admixture of plasmatic cells and macrophages. Outside of the vessels the infiltrates are found in the cerebray cortex, as well as in the pons varolii, and consist of microglia, plasmatic cells, and neutrophyls. Degenerative and necrotic foci are frequently found in the center of such infiltrates.

Hyperemia of the vessels and cellular infiltrates are found in all sections of the cerebrum and the upper sections of the spinal cord. Degenerative changes of the nerve cells, as well as necrotic foci, are recorded primarily in the cerebral cortex, pon varolii, basal ganglions, and the medulla oblongata.

Comparing the pathohistological picture of St. Louis encephalitis with the changes peculiar to the economo type of lethargic encephalitis, it may be pointed out that in the former case the inflammation foci are more widely defused in the cerebral cortex while the foci of degeneration and necrosis are considerably more pronounced.

In addition to the changes in the central nervous system, the St. Louis encephalitis reveals a considerably more pronounced swelling and necrosis of the epithelium of the kidney canaliculi than in the case of Japanese encephalitis (L. A. Silber, 1945).

Laboratory diagnosis. A reliable diagnosis of the American encephalitis can be made only by laboratory methods which amount to the isolation of the virus and serological investigations.

The most reliable method of isolating the virus in man is the method of intracerebral infection of white mice.

The patient's blood and cerebrospinal fluid are used for such investigations, and in the case of dead bodies samples of the brain are used.

The intravital isolation of the virus from the blood and cerebrospinal fluid of the patient is very difficult. In such cases the method of consecutive passages is resorted to. The best time for isolating the virus from the blood is between the 3rd and 7th day of the disease. After that or at the very onset of the disease it is, as a rule, impossible to isolate the virus from the patient's blood.

It is quite easy to isolate the virus from the brain of dead persons. Pieces of the brain are emulsified in a physiologic solution in wuch a way as to produce a 10% emulsion, 0.03 ml of which is then injected intracerebrally into white mice.

There are 2 methods of finding specific antibodies: a complement fixation reaction and a neutral reaction.

The complement-binding antibodies appear in the patients at the end of the first week of the disease, and the virus-neutralizing antibodies a month later. These periods should be taken into account when making a laboratory diagnosis. The complement-fixation and neutral reactions are produced by the usual methods. Bearing in mind the results, attention should be focused on the fact that the St. Louis virus is immunologically related to the viruses of the Japanese and Nile encephalitis.

The serum of Japanese encephalitis patients therefore neutralizes the St. Louis virus but in lower titers than the homological strain, and the serum of the St. Louis encephalitis patients partially neutralizes the virus of the West Nile encephalitis.

Treatment. There are no specific methods of treatment.

Prophylaxis. The principal prophylactic methods against the American St. Louis encephalitis is the fight against the carrier mosquitoes.

The measures designed to exterminate the mosquitoes and prevent their breeding should also be accompanied by protective measures against their bites.

In view of the available indications that certain types of ticks are epidemiologically effective, measures should be taken to exterminate them and prevent their bites.

Specific prophylactic measures against the American St. Louis encephalitis have not yet been fully developed. A dead vaccine inactivated by formalin (Sabin, 1943) and a vaccine prepared from a virus inactivated by ultraviolet radiation are now in the stage of experimental investigation.

The American Western Equine Encephalomyelitis

Definition. The American western equine encephalomyelitis is a viral epizootic disease of horses and mules. The virus is pathogenic for men and causes a disease similar to the American St. Louis encephalitis.

History. Seasonal epidemics of equine and mule encephalomyelitis have been recorded in the U.S. for a long time.

A large-scale epidemic of equine encephalomyelitis was recorded in 1930 in California. In their study of that epidemic, Meyer, Herring, and Howitt (1931) were the first to isolate a filtrable virus, the causative agent, from the brains of horses.

In 1932 Meyer reported for the first time of three cases of encephalitis in children who had had close contact with the sick horses.

A large-scale equine encephalomyelitis broke out in Minnesota in 1934 and lasted until 1937. During that period 41,159 of the state's 737,000 horses were affected by the disease and 2,200 of them died. Six cases of people affected by that epidemic were also recorded during that period.

A large number of people were affected by the disease in California in 1937, and 40 of them died.

In 1938 a large-scale epidemic of equine encephalomyelitis broke out in Massachussetts and Rhode Island, where the high incidence of the disease among horses was paralleled by a number of cases among people.

In that same year Howitt was the first to isolate the virus of the western equine encephalomyelitis from the brains of the dead horses and the blood of human patients.

The largest epidemic brought about by the virus of the western equine encephalomyelitis took place in 1941 in North Dakota, Minnesota, and the adjacent Canadian provinces. The epidemic affected more than 3,000 people and the mortality rate was between 8 and 15% (Olitzky and Casals, 1952).

In the following years the disease was periodically recorded in certain western states of the U.S.

Etiology. The agent of the disease is the filtrable virus Polyvectus occidentalis. The virus filters through the Berkefeld candles N. V, and W and through the Zeits filters, and has a diameter of 25-40$M\mu$.

Seen through an electron microscope, the virus of the western equine encephalomyelitis appears like a round particle with irregular edges.

By its antigenic structure the agent is related to that of the American eastern equine encephalomyelitis, which is revealed by a complement-fixation reaction. This relationship could not be established by neutralization and chiasmic resistance tests.

The virus has a definite stability. Under refrigeration conditions its maximum stability can be achieved at pH = 7-8.5. In a medium with a pH below 6.5 the virus is rapidly inactivated. At a temperature of 60° the virus is destroyed in 10 minutes; but it can be preserved for a long time in a 0.5% phenol solution and a 0.05% mercuric chloride solution. Thiolic acid ester and phenyl-mercuric

borate can be used as virus-preservatives (in 1:10,000 and 1:50,000 solutions). The virus can be well-preserved in a cold 50% buffer glycerin at pH = 7.4-7.5, as well as in a frozen state (Olitsky and Casals, 1952).

Many animals and birds are susceptible to the western equine encephalmyelitis: horses, monkeys, rats, hamsters, squirrels, dogs, reindeer, gophers, calves, goats, black grouse, and pigeons. Among the experimental animals, white mice, guinea pigs, and rabbits are susceptible. Sheep and cats are among the resistant animals.

Domestic and certain types of wild fowl develop virusemia after the affection but without any symptoms of the disease (Hammond and Reeves, 1945).

A white mouse is the most convenient experimental model. When infected intracerebrally, the virus infects and kills the mouse in a 10^{-8} dilution, and intranasally in a 10^{-3} dilution. Larger doses are required for intra-abdominal and intramuscular infections.

In 2 to 6 days after the intracerebral injection of the virus, the mice reveal symptoms of meningo-encephalomyelitis: a generalized spastic contraction of the muscles, spastic paralysis, and uncoordinated movements. Death may come on in a few hours after the appearance of the first symptoms of the disease but more frequently in one to 2 days.

Epidemiology. The reservoir of the virus in nature has not been finally established, but it is assumed that it resides in various wild birds and animals.

It has been established that domestic fowl, particularly young chicks, reveal (viremia) without any symptoms of the disease after being infected with the virus by mosquitoes. Similar data have been obtained after the infection of certain types of wild birds.

Wild ducks and geese, hawks, storks, burrow owls, pheasants, sparrows, and quail were found to be susceptible to the virus (Seaburton and Berry, 1941; Titser, 1938; Rockhill and Clerk, 1939).

Investigating the blood of sparrows caught in the state of New Jersey, Holden isolated 2 virus stems of the western equine encephalomyelitis (1955). Virus-neutralizing antibodies were found in the sera of 12 domestic fowl in the same area.

There is reason to believe also that numerous types of wild animals are the reservoir of the virus, as it has been found that forest and furry rats are susceptible to the virus (Grundman, 1943).

It has now been established that certain types of mosquitoes (Culex tarsalis, Aedes dorsalis, Aedes aegypti, Aedes vexans, Aedes taeniarhynchus, etc.) and ticks (Dermacentor variabilis, Dermacentor andersoni, etc.) experimentally infected with the virus of western encephalomyelitis can infect horses and various experimental animals (Kelser, 1933; Simons, Reynolds and Cornell, 1930). Seaburton and Berry (1941) showed that the virus of the disease can be transmitted from infected guinea pigs to ground squirrels through forest ticks

(Dermacentor andersoni). It was also established that the ticks transmit the virus to their progeny.

In 1941 Hammond isolated the virus from Culex Tarsalis mosquitoes caught in the open.

Following large-scale epizootic and epidemic outbreaks of western equine encephalomyelitis in the Mississippi River valley, a search was carried out for the virus reservoir in the inter-epidemic period. As a result, 4 stems of the virus were isolated from the Culex tarsalis mosquitoes and one stem from the Aedes vexans mosquitoes (Barros, 1954).

At the same time, the neutral reaction produced with the blood serum of the domestic animals and birds was found to be positive in 18% of the cases, and with the serum of wild birds in 5%.

According to Olitsky and Casals (1952), the infective agent of the western equine encephalomyelitis circulates in the following manner: the bird ticks maintain the virus under natural conditions and the mosquitoes transmit it to other birds, as well as from birds to horses; the same type of mosquitoes carry the virus among people.

The possibility of an experimental transmission of the virus by mosquitoes and ticks to animals and birds, as well as their capacity for spontaneous infection, justifies the assumption that they are the virus carriers.

The possibility of other types of carriers is not ruled out. Kitselman and Grundman, for example, established (1940) that fleas (Triatoma sanguisuga) can be spontaneously infected with the virus of the western encephalomyelitis.

Further research will produce more definite information in regard to both the reservoir of the virus in nature and the methods of its circulation. It is already possible to assume, however, that the western equine encephalomyelitis will be grouped with the infectious diseases characterized by natural focal aspects.

Horses and domestic fowl can be infected in natural foci by mosquitoes and ticks and become secondary reservoirs of the virus. Being close to man, the virus-carrying sick horses and domestic fowl are particularly dangerous from an epidemiological point of view. People are apparently infected by mosquito bites.

As a rule, people are affected by the disease during the epizootics among horses. Individual cases are also known of people being affected by the disease which is not connected with epizootics.

The largest epidemic of equine encephalomyelitis affecting 509 people occurred in 1941 in Manitoba, Canada.

Epizootics of western encephalomyelitis among horses, as well as outbreaks of the disease among people, occur primarily in the western states of the U.S. and the adjacent Canadian areas, the highest incidence being observed in the rural areas.

Cases of western equine encephalomyelitis are very seldom recorded outside of the mentioned areas.

Worthy of attention is the report that the virus stems isolated from wild rodents and Dermacentor marginatus ticks in recent years in Czechoslovakia were found to be identical to the virus of the American western equine encephalomyelitis (according to A. A. Smorodinstyev). The above fact is of great interest, as the American western equine encephalomyelitis is not yet well known in Europe.

The incidence of western equine encephalomyelitis is strictly seasonal: all the known cases of the disease were recorded between the middle of July and the middle of September. The disease may also be called an occupational disease: it affects primarily workers in agriculture living in the epizootic areas and persons working in the open air.

Children account for a considerable percentage of the patients. Forty of the 509 people infected in Manitobe were children (27 under one year and 13 under 4).

The clinical picture. The clinical picture of the American western encephalomyelitis resembles the St. Louis encephalitis. The incubation period lasts from 5 to 10 days and less often to 21 days.

The prodromal period is characterized by slight headaches, drowsiness, fever, and nausea. Then the temperature suddenly rises to 40-41° and remains at that level from 7 to 10 days. The nervous system becomes disordered: severe headache, insomnia, and vomiting.

Drowsiness, speech impairments, ataxia, nystagmus, a tremor of the extremities, and convulsions may be observed when the disease is at its highest point. Observed also are occasional hallucinations, loss of memory, and even a coma. Paralysis of the extremities develops in 10-15% of the cases. Considerably less frequent is paralysis of the eye muscles (Olitsky and Casals, 1952).

Neutrophylic leucocytosis is, as a rule, found in the leucocytes with the total quantity of leucocytes ranging from 10,000 to 16,000 per 1 ml^3.

Pleocytosis (up to 400 cells and more) is found in the cerebrospinal fluid, and the amount of albumin increases; the sugar content rises insignificantly or remains unchanged.

Occasionally the course of the disease becomes abortive. In such cases the 20-30 hour fever and the headaches are followed by recovery. The disease is frequently observed in indistinct forms without any pronounced clinical symptoms, but with an accumulation of virus-neutralizing antibodies in the blood.

In favorable cases the disease, as a rule, ends in complete recovery. The mortality among adults does not exceed 8%, but among children it goes up to 20%.

Pathological anatomy. Macroscopic and microscopic investigations reveal changes in the central nervous system evidencing occurrences of meningo-encephalitis which resemble those occurring in St. Louis encephalitis. When the spinal cord is affected, small foci of

pathological changes are noted in the upper area of the neck. Infection sources characterized by a focal accumulation of glial cells, perivascular lymphatic infiltration, and a necrosis of the nerve cells appear in the gray substance. Occasionally there is a diffuse infiltration of the gray substance of the spinal cord with an accumulation of neutrophyls and mononuclears. Separate sources of microglial accumulations and myelomalacia without an inflammatory process are found in the white substance of the spinal cord (Olitsky and Casals, 1952).

Diagnosis. The laboratory methods of diagnosing the American equine encephalomyelitis are the same as those used for the St. Louis encephalitis.

Treatment. There are no specific methods of treatment at present.

The use of hyperimmune serum in experiments on animals is found to be effective only when it is introduced before the symptoms of the disease appear. The introduction of the serum after the appearance of the clinical symptoms is, with rare exceptions, useless (Olitsky, Slessinger and Morgan, 1943).

Sulfa drugs were found to be ineffective. There is no available published materials on the treatment with antibiotics.

Prophylaxis. A formalin-treated vaccine prepared from a virus cultivated on chicken embryos is now used in the T.S. for the specific prophylactic treatment of horses. This vaccine was approved also for people. Specific antibodies were revealed in the blood serum of people after 2 vaccinations. The general reaction to the vaccine was moderate. A bivalent formalin-treated vaccine designed as a prophylactic measure against western and eastern encephalomyelitis has now been developed in the U.S. (Bard and Finklestein, 1940). But the effectiveness of the vaccine for the immunization of people must still be tested in epidemiological experiments.

The use of a specific antiserum as a prophylactic measure against the disease in man has not produced any satisfactory results.

The measures designed to exterminate the mosquitoes and protect the people from their bites are the same as those used in other diseases transmitted by these carriers.

American Eastern Equine Encephalomyelitis

Definition. The American eastern equine encephalomyelitis is a viral epizootic disease of horses, mules, and birds. The virus is highly pathogenic also for man; it brings about a grave disease which is characterized by the inflammation and destruction of the cells of the central nervous system.

History. The first cases of equine encephalomyelitis in the eastern states of the U.S. (Virginia, Delaware, New Jersey, and Maryland) were recorded in 1933. In that same year Ten-Broeck and Merrill isolated the virus from the brain of dead animals.

In 1938 Fazerhil, Webster, and Wright first isolated the virus from the brain of a person who had died of that disease.

A large-scale epidemic brought about by the agent of the eastern equine encephalomyelitis broke out in 1938 in Massachusetts. A total of 34 cases were recorded, mostly among children. The mortality in that outbreak went up to 74% (Olitsky and Casals, 1952).

Isolated cases of people infected with that disease were recorded in Texas and Indiana in the following years (1939, 1941, and 1942).

Identical or similar strains of the virus were isolated in Argentina and Brazil.

Etiology. The causative agent of the disease is a filtrable virus Polyvectus orientalis. The virus filters through the N, V, and W Berkefeld candles and Zeits filters. The size of the virus ranges between 20 and 30 mμ. The virus can be easily produced on chicken embryos and tissue cultures. According to an available description, the virus of the eastern equine encephalomyelitis is cultivated on gambusia embryos, whereby the latter are placed in a 3-5 ml medium consisting of 5 parts of Hanks saline solution and 1 part of an ultrafiltrate of a bull's serum (Sorett, Sanders, 1954).

By its biological characteristics the virus of the eastern equine encephalomyelitis is closely related to that of the western encephalomyelitis. But both viruses are comparatively easy to differentiate by the complement-fixation reaction, as well as in tests with chiasmic neutralization.

V. M. Zhdanov (1953) considers it necessary to single out the following geographic varieties of the eastern encephalitis virus:

a) Polyvectus orientalis var. nordica, confined to the eastern areas of North America;

b) Polyvectus orientalis var. brasiliensis, confined to Brazil;

c) Polyvectus orientalis var. argentinae, confined to Argentina.

The above-listed types of virus differ both by the degree of pathogenicity as well as by the antigenic structure.

Monkeys, cats, sheep, hedgehogs, pigeons, and quail are susceptible to the eastern encephalomyelitis virus, and other experimental animals -- white mice and guinea pigs. The pathogenicity of the eastern encephalomyelitis virus is considerably greater than that of the western encephalomyelitis.

Epidemiology. Eastern encephalomyelitis is now prevalent among horses and mules in the eastern states of the U.S., Canada (Ontario), Mexico, Panama, Cuba, Brazil, and Argentina.

Cases of both eastern and western equine encephalomyelitis have been recorded in 3 states (Alabama, Michigan, and Texas).

The reservoir of the virus in nature has not yet been finally established. It is assumed that birds are the reservoir of the infection.

Infected birds were found in 1948 among the pheasants and pigeons caught in the endemic areas; the virus of the eastern encephalomyelitis was isolated from the birds' blood (Olitsky and Casals, 1952). Ten-Broeck (1940) observed viremia in birds without any clear symptoms of the disease.

Following an investigation of the blood of 347 wild birds caught in Louisiana, Kissling, Chamberlin, Sikes, and Eidson (1954) showed that some types of wild birds contain the virus of the eastern equine encephalomyelitis in their blood. It was possible to reproduce the disease in an experimental infection of wild birds by exposing them to infected Aedes aegypti and Aedes triseriatus mosquitoes. Two to four days after the infection virusemia was found in all the birds, and an increasing number of virus-neutralizing antibodies was observed in the serum of the surviving birds. A lethal form of the infection was observed in some of the birds.

Horses apparently represent an additional reservoir of the virus in nature.

Horses were infected by exposing them to infected Aedes aegypti mosquitoes. Serious diseases ending in death frequently developed as a result. An accumulation of virus-neutralizing antibodies was found in the serum of all the animals. The attempt to infect horses by exposing them to mosquitoes which had fed on sick animals ended in failure (Kissling, Chamberlin, Edison, Sikes, Buccai, 1954). According to some opinion (Schaeffer, Arnold, 1954), horses cannot serve as the sources of infection of mosquitoes, as the virus titer in their blood is relatively low.

It is now known that the Aedes solicitans, Aedes vexan, Aedes cantator, and Culex restuans mosquitoes, as well as the Dermacentor andersoni ticks, can be infected with the virus of the eastern equine encephalomyelitis under experimental conditions (Zhdanov, 1953; Olitsky and Casals, 1952).

It was possible to infect the Aedes aegypti and Aedes triseriatus mosquitoes with the virus of the eastern and western encephalomyelitis by feeding on infected chicks under experimental conditions (Chamberlin, Corristan, and Sikes, 1954).

Spontaneous infectiveness with the virus of the eastern equine encephalomyelitis was established in the Culiseta melanura and Mansonia perturbans mosquitoes, as well as in the Dermanyssus gallinae ticks (Howitt, 1949, Holden, Miller and Dobbinsk, 1954). It was also proved that the virus is capable of multiplying in the Aedes sollicitans mosquitoes. All this prompts the assumption that mosquitoes and ticks are the carriers of the virus.

People are apparently infected by the bites of the infected mosquitoes and ticks.

Eastern encephalomyelitis is strictly seasonal: all the observed cases of the disease occurred between July and October, and the highest incidence was noted in August. The outbreak of the disease among people is, as a rule, preceeded by epizootics among horses and mules. A large percentage of the patients are children. Thus about 70% of the people suffering from eastern equine encephalomyelitis were children under 10. Men and women are equally susceptible to the disease.

The clinical picture. The incubation period has not been determined. The course of the disease is usually painful and consists of 2 phases. The first clinical symptoms appear suddenly. The patients complain of severe headaches accompanied by nausea and vomiting. The fever lasting 24-36 hours is followed by a slight alleviation.

This is followed by the second phase of the disease. The temperature rises to 40-41° and is accompanied by increasing drowsiness. The disease progresses rapidly, the patients develop convulsions, rigidity of the occipital muscles, and a paralysis of the extremities. The disease is frequently fatal. An opistotonos or coma is occasionally observed (Olitsky and Casals, 1952).

Pleocytosis is found in the cerebral spinal fluid (up to 1,000 cells per 1 ml^3); neutrophyls are predominant in the early stage of the disease and monanuclears later on. The Albumin content increases and the quantity of sugar remains unchanged.

The acute manifestations of the disease last from several days to 3 weeks, averaging about 1 week. The mortality during the outbreaks was as high as 74%. The various after-effects remaining after recovery range from emotional instability to various types of paralysis and mental derangement (Farber, 1940). In addition to the cases revealing an exceptionally serious clinical picture, the disease may also take an imperceptible course (Olitsky and Morgan, 1939).

Pathological anatomy. A macroscopic investigation reveals a hyperemia of the internal organs and a pulmonary adema. A stasis, adema, and depression of the cerebral gyrus is noted in the brain. A microscopic investigation reveals an inflammation of the cerebral and spinal-cord membranes and necrotic foci in the cerebrum, mostly in the basal ganglions and the stem. The spinal cord frequently remains unchanged.

Laboratory diagnosis. Basically, the laboratory diagnosis is not different from the one of the American St. Louis encephalitis or the western equine encephalomyelitis.

Treatment. There are no specific methods of treatment. Symptomatic therapy is used and complete bed rest prescribed.

Prophylaxis. A formalin-treated vaccine prepared from a virus produced on chicken embryos has been successfully used in the U.S. for the specific prophylaxis of the disease in horses.

The vaccine has not yet been tested in large-scale epidemiological experiments and is not recommended for the mass immunization of people.

The immunization of laboratory workers showed that the vaccine was nonreactive. The vaccinated workers did not contract the disease.

In experimental conditions, specific anti-sera impeded the development of the disease: but these have not yet been used as prophylactic measures against the disease in people.

The measures designed against mosquitoes and ticks are the same as those used in other diseases transmitted by these carriers.

Venezuelan Equine Encephalomyelitis

Definition. The Venezuelan equine encephalomyelitis is an acute viral epizootic disease of horses and mules.

The virus is pathogenic in people, bringing about encephalitis, usually in mild form.

History. The epizootic of the Venezuelan equine encephalomyelitis among horses and mules was first recorded in 1935 in Colombia.

A large-scale epizootic broke out in Venezuela in 1938.

The virus of the disease was isolated in 1938 by Beck and Bykov from the brain of the dead animals. In the following years encephalomyelitis epizootics occurred in Ecuador, Panama, and on Trinidad Island.

Cases of people being affected by the disease were first reported by Casals, Curnen, and Thomas (1943). Those were mild cases involving laboratory workers. Two cases ending in the death of the infected people occurred on Trinidad island in 1943. Infections of people were observed also in Argentina in 1944.

Etiology. The causative agent of the disease is the filtrable virus Polyvectus venezuelensis.

The virus filters through the N, V, and W Berkefeld candles and Zeits filters and can be preserved for a long time in a 50% buffer solution of glycerin in a refrigerator and in a frozen state.

The virus is easily cultivable on chicken embryos and in tissue cultures, particularly in Erlinmeyer test tubes by the Enders method in suspended pieces of uterine tissue. After 15 passages through the tissue culture the pathogenicity of the virus in white mice, when introduced intracerebrally, was reduced. The virus titration in tissue culture was found to be a less sensitive method than the titration on white mice (Gaydusek, etc., 1954).

The virus is pathogenic in horses, mules, mice, guinea pigs, rabbits, rats, dogs, cats, sheep, and goats. Among the animals unsusceptible to it are cattle and hogs. The white mouse is an experimental model.

White mice are sensitive to all methods of infection: intraperitoneal, intravenous, intracerebral, and subcutaneous. By all these methods the infected mice reveal the typical symptoms of the infection of the central nervous system and then die. In the course of the disease the virus is isolated from the cerebrum. The mice die faster when the intra-cerebral method of infection is used.

The guinea pig is usually susceptible to the virus of the venezuelan encephalomyelitis.

About 12 to 24 hours after the intraperitoneal infection they develop a fever, and after 48 to 96 hours they are dead.

Rabbits are relatively more resistant. The disease cannot always be reproduced in them, even by an intracerebral infection with large doses of the virus. In some cases, however, the rabbits develop a lethal disease similar to one observed in guinea pigs (Sanmartin-Barberi, Groot, Osorno-Mesa, 1954).

Epidemiology. The reservoir of the virus in nature is not known. The methods of transmitting the virus to man have not been adquately studied.

It was noted that wherever the disease broke out among people there were many mosquitoes about. Thus during the 1952 outbreak of encephalomyelitis in Colombia in an inhabited point where cases of the disease had been recorded, there were many Aedes aegypti and Culex fatigans mosquitoes. The extermination of the mosquitoes with DDT during the outbreak reduced the incidence to a considerable extent (Sanmartin-Barberi, etc., 1954).

Some people believe that the virus of the Venezuelan equine encephalomyelitis may also be carried by other types of mosquitoes, particularly Aedes taeniarhynchus and Mansonia titillans (Gilliard, 1944).

It was shown under laboratory conditions that the Aedes aegypti and Culex fatigans mosquitoes were capable of transmitting the virus 8 days after having fed on infected white mice. It has not yet been established whether the mosquitoes can be spontaneously infected with the virus of the Venezuelan equine encephalomyelitis.

People are infected with the disease as a rule in the spring-summer period (March-June) and mostly in the rural areas.

Descriptions of several laboratory cases of infection were published (Casals, 1943; Koprowski and Cox, 1947, etc.). It is assumed that under those conditions the infection was brought about by aerogenic methods.

Worthy of attention from the epizootic and epidemiological points of view is the investigation of the possibility of contactile transmission of the disease among white mice (Sanmartin-Barberi, etc., 1954). It was found that sick white mice did not transmit the virus to the healthy mice that were kept in the same cage with them.

The clinical picture. The incubation period has not been established. In cases of intra-laboratory infections it did not exceed 24-48 hours (Sanmartin-Barberi, etc., 1954).

The disease is characterized by a sudden onset. After a slight exhaustion, the patients develop chills followed by fever. The temperature rises to 38.8-39.8° and sometimes higher. The patients complain of headaches, muscular pain, and frequently develop nausea and vomiting and drowsiness. An investigation of the blood reveals leucopenia. The critical period of the disease and the fever lasts 2-3 days, less often 5 days. In severe cases the disease may be protracted to 7-8 days and end in recovery. The convalesing patients feel weak for 2-3 weeks after the disease.

In 2 of the studied cases that occurred on Trinidad island the disease was very serious with symptoms of encephalitis which were followed by coma and death.

It is believed that in addition to the clinically pronounced cases there are also indistinct forms of the disease which remain undiagnosed. This is indicated by the frequent discovery of neutralizing antibodies in people who did not endure a clinically pronounced disease (Olitsky and Casals, 1952).

The pathological anatomy of the Venezuelan encephalomyelitis has not been adquately studied.

Diagnosis. The diagnosis of the disease is made only by laboratory methods. The virus can be isolated from the blood of the patient's nasopharynx when the disease is in full swing. In lethal cases, pieces of the brain can be used for isolating the virus. The virus is isolated by the generally accepted methods.

Complement-fixing and virus-neutralizing antibodies are found in the patients during the recuperation period.

Treatment. There are no specific methods of treatment. Symptomatic therapy is used.

Prophylactic measures. A formalin-treated vaccine prepared from a virus developed on chicken embryos was used in Venezuela for the specific prophylaxis against the disease in horses.

The measures against the mosquitoes carrying the Venezuelan encephalitis virus are the same as those used for the other diseases transmitted by these insects.

When handling the virus of the Venezuelan encephalitis in a laboratory, a cotton and gauze mask should be used to protect the respiratory organs from the infected material.

Australian Encephalitis (X-Disease)

Definition. Australian encephalitis is an acute viral disease prevalent in Australia.

History. An epidemic of acute encephalitis, affecting 134 people, occurred in the summer of 1917 in Australia (New South Wales). About half of those affected were children under 5. The mortality of that disease was as high as 70%.

The encephalitis epidemic recurred in the summer of 1918. Cases of that disease were recorded also in 1922, 1925, and 1926, but in a milder form.

The virus was isolated in 1917 by Cleland and Campbell from the brain of the dead people.

An outbreak of severe encephalitis with a high mortality occurred in 1952 in Australia (Murray Valley, North Victoria). French isolated the virus from patients in 1952. Several cases of the encephalitis disease occurred at the same time in South Australia. Miles, Fowler, and Goalis also isolated the virus of the brain of the dead people.

Etiology. The agent of the disease is a filtrable virus Encephalophilus australis. It has not been adequately studied, as it was lost soon after it had been isolated. The virus has been classified as Encephalophilus on the basis of the pathogenisis and the epidemiological characteristics of the diseases it causes (Zhdanov, 1953).

The serological characteristics of the virus and its immunological relationship with the other viruses are still unknown.

The virus is easily cultivable on chicken embryos and is pathogenic in man, sheep, horses, cows, monkeys, calves, and mice when introduced intracerebrally.

Infected intracerebrally with the virus, monkeys (Macacus rhesus and Macacus cynomolgus) developed encephalitis symptoms after 3 to 5 days of incubation: general numbness, muscular weakness, disordered coordination of movements and tremor. Any irritation of the animals brought about convulsions. Increasing weakness and symptoms of stupor ended in the death of the monkeys within 2 to 6 days.

The pathoanatomical changes in the monkeys were characterized by a hyperemia of the cerebral and cerebellum membranes, the formation of vascular sleeves in the gray substance, and petechial hemorrhages.

Sheep were found to be less susceptible than monkeys. But when intracerebrally infected, they also developed symptoms of encephalitis after 3 to 12 days ending in death.

Dogs, cats, rabbits, guinea pigs, and birds were found to be unsusceptible to the disease.

The relationship between the virus isolated in the Murray Valley and the agent of the Japanese encephalitis was manifested both in chiasmic neutral reactions and in complement-fixation reactions. Clinically, the diseases were found to be quite similar to the Australian

encephalitis (X-disease) during the 1917-1918 epidemics. Burnet (1952) isolated that disease into an independent nosological unit and called it the Murray Valleyencephalitis, but there are reasons to believe that an outbreak of Australian encephalitis occurred in 1952 (Miles, 1953). In their experiments with the serum of people surviving the infection of 1917-1918, McLean and Stevenson (1954) proved the immunological identity between the viruses of the Australian encephalitis and the Murray Valley encephalitis.

Epidemiology. One of the characteristics of the Australian encephalitis is that it is strictly seasonal. The disease is recorded between January and April, with most of the cases occurring in February and March. This coincides with the summer-autumn period in our hemisphere.

Another epidemiological characteristic noted in the 1917-1918 epidemics was that all the diseases occurred in places where the climate was dry. This prompts the assumption that the climate affects the emergence and spread of the diseases.

Children were more frequently affected than adults. Men were more frequently affected than women.

The antibodies against the virus were found in horses and dogs.

It has been suggested that the disease is transmitted by contact (Cleland and Campbell). The possibility that the disease can be transmitted by suctorial anthropods is not ruled out.

It was established that the Culex anuliorstris, Culex fatigans, Aedes vigilax, and Aedes vittiges mosquitoes are capable of being infected with the virus of the Murray Valley encephalitis under laboratory conditions (McLean, 1953). It was also found that the domestic fowl in the endemic areas contained antibodies for the virus of the Murray Valley encephalitis (Millis, 1954).

Bearing in mind that the Australian encephalitis and the Murrey Valley encephalitis are apparently identical diseases, the above-cited data are of great interest. This exhausts the meager information available in literature on the epidemiology of the Australian encephalitis.

The clinical picture. The incubation period lasts 5 to 12 days. The occasional prodromal symptoms are manifested in headaches, general irritability, and weakness on the extremities.

The initial symptoms of the disease in children are vomiting, rising temperature, and spasms; in adults the symptoms are headaches, pronounced drowsiness, occasionally developing into lethargy, muscular weakness, and disordered coordination of movements.

The temperature rises to 39-40.5°. Later developments include a dulled mind, uncontrolled movements of the extremities, tremors, tonic spasms, facial myospasms, and hiccuping.

The craniocerebral nerves, with the exception of those connected with the visceral functions, are not affected, which is an important distinction from lethargic encephalitis.

The pleocytosis in the spinal-cord fluid does not contain any pathological elements; a moderate leucocytosis is found in the blood.

In lethal cases the disease lasts 4 to 5 days; whenever the patients recover, the acute symptoms disappear in 10-12 days.

Australian encephalitis is characterized by a very high mortality, going up to 70% (94 of the 134 patients died during the 1917-1918 epidemic).

Pathological anatomy. An investigation of the brain revealed the following changes: vascular hyperemia, perivascular infiltration, and capillary hemorrhages. In addition, necrotic foci were observed in the cerebral cortex, pons varolii, and cerebellum. Particularly affected are the Pourkinje cells in the cerebellum, which is recorded also in the Scotland sheep encephalomyelitis.

There is no information available in the reference literature on the laboratory diagnosis, treatment, and prophylaxis of Australian encephalitis.

Scotland Sheep Encephalomyelitis (Louping Ill)

Scotland encephalomyelitis is a viral epizootic disease of sheep characterized by a cerebellar ataxia. The virus is pathogenic also in man, producing mild forms of encephalitis.

History. Scotland sheep encephalomyelitis is prevalent in Scotland and in Northern England, where it has been known since 1807.

The agent of the disease was discovered by Poole, Brownley, and Wilson in 1930.

In 1933 Rivers and Schwentker first reported the disease in people who had been infected under laboratory conditions.

In 1944 Casals established a close serological relationship between the virus of the Scotland sheep encephalomyelitis with the virus of the vernal tick-borne encephalitis.

In the same year L. A. Silber and A. K. Shubladze showed that the virus isolated from ticks in the western areas of the USSR was quite similar to the agent of sheep encephalomyelitis.

Etiology. The causative agent of the disease is a filtrable virus Encephalophilus scotticus.

The antigenic structure of the virus is quite similar to that of the virus isolated from encephalitis patients in the western areas of the USSR. Both viruses were found to be exceptionally similar in their immunological characteristics and they cannot be accurately differentiated by the neutral-reaction and complement-fixation reaction titers.

There is no unanimous agreement now as to whether both viruses should be considered identical or classified as different types.

V. M. Zhdanov (1953) singles out the virus isolated by L. A. Silber as a separate type, Encephalophilus occidentalis, but points out that that virus differs from the virus of the Scotland encephalomyelitis only from an ecological point of view. Besides, the virus of the Scotland encephalomyelitis is immunologically closely related to the agent of the tick-borne vernal encephalitis, from which it can be differentiated by the neutral-reaction and complement-fixation titers only with some difficulty.

The virus of the Scotland sheep encephalomyelitis passes through the N, V, and W Berkefeld candles, the Zeits filters and the Chamberlin L_2 and L_3 filters; its size is 15-20 mμ.

The virus is rapidly inactivated at room temperature. In brain tissue suspensions at a temperature of 80° the virus is inactivated in 30 seconds, and at 60° in 2 minutes.

A 1:250 dilution of hydrogen peroxide kills the virus in 4 hours, and a 1:2000 dilution of Javel water in 3 hours.

The virus can be kept up to 160 days in a 50% glycerin buffer solution. A + 4° temperature and Ph = 7.5-8.5 are suitable for preserving the virus.

The virus can be well cultivated on a chorioallantoic membrane of a chicken embryo, as well as in a medium of chicken embryos suspended in a mixture of monkey serum and a tirode solution.

Sheep, monkeys, pigs, calves, hamsters, and field mice are susceptible to the disease. The white mouse is a laboratory model. The virus is not pathogenic in guinea pigs or rabbits.

A more complete experimental study of the disease was made in the case of sheep which are exceptionally vulnerable to this virus. Infection occurs when the virus is introduced into the cerebrum or spinal cord, into the sciatic nerve, nose, and conjunctival sac.

A clinical manifestation of the disease in sheep is the affection of the cerebellum. The sick animals reveal a strong tremor of the head and swift jerky movements around a circle. Their walk is unsteady and their movements uncoordinated. The temperature rapidly rises to a high level and is followed by spasms, paresis, and paralysis. The disease is frequently fatal to the animals.

In addition to its painful course, the disease occasionally takes on chronic and abortive forms.

When infected intracerebrally with a virus suspension, white mice reveal symptoms of stimulation after an incubation of 5-6 days; this is followed by a paralysis and 8 days after the infection the animals die.

In the case of intracerebrally-infected monkeys, the temperature rises to 39-40° after 4-5 days of incubation, and the subjects develop a swaying walk and a weakness in the extremities. The animals die 10 days after the onset of the disease.

White mice and monkeys can be infected also intranasally, subcutaneously, and intraperitonially.

Epidemiology. Sheep, and probably wild rodents, are the natural reservoir of the virus in nature.

The carriers are Ixodes ricinus and Rhipicephalus appendiculatus ticks; and their capacity for the ovarial transmission of the virus has not been established.

The disease is prevalent among the sheep in Scotland, England, and Western Europe.

The epizootics are strictly seasonal, as the disease is recorded only during the spring period (March, April, May).

Man is susceptible to the louping ill virus. Infection is produced by the bites of infected ticks; contact with sick sheep is absolutely safe. In view of the fact that people's susceptibility to the virus is weak and the major carrier, the Ixodes ricinus tick, seldom attacks people, the outbreak of the disease among people under ordinary conditions is very rare.

Four cases of people infected with encephalitis under natural conditions were described by English researchers in 1948-1949. In 1949, Czechoslovak researchers (Glodsal and Galliya) reported an outbreak of Scotland encephalomyelitis in Czechoslovakia among people (38 cases).

But the disease could probably become more widespread through a close and lengthy contact between the people and the biotopes of ixodian ticks.

The infections occurring in laboratories are assumed to have been brought about by aerogenic methods (Olitsky and Casals, 1952).

The clinical picture. The incubation period has not been precisely determined; it is assumed that it lasts about 2 weeks.

The clinical picture of the disease consists of 2 phases. Fever, headaches, nausea, vomiting, indisposition, and weakness are observed in the first phase, which lasts a week. This is followed by an improvement lasting a week or longer. The eventual development of the second phase is accompanied by a rising temperature, headaches, nausea, and vomiting. There is increasing drowsiness, diplopia, and a rigidity of the occipital muscles and Kernig symptoms are noted. The tendon reflexes at the upper and lower extremities become weaker. The patient's mind may become dulled (Glazunov and Popova, 1948; Olitsky and Casals, 1942).

Leucocytosis (up to 17,000 leucocytes per 1_{MM}^3) is found in the blood, and a mononuclear pleocytosis and an increased albumin content in the spinalcord fluid. The intercranial pressure is higher.

The disease lasts 4-5 weeks and, as a rule, ends in complete recovery.

There are indications that, in addition to clinically pronounced cases, Scotland encephalomyelitis may be found in people in an asymptomatic form.

The disease leaves a stable immunity in the survivors.

Pathological anatomy. The pathohistological changes in the brain during Scotland encephalomyelitis are very similar to those occurring

in various forms of encephalitis and are expressed in various forms of inflammations.

A distinctive feature is a clearly pronounced destruction of the Pourkinje cells in the cerebellum.

Diagnosis. Laboratory data are decisive in diagnosing the disease in people.

The virus can be isolated from the blood of the patient's cerebrospinal fluid and from the cerebral tissue after an autopsy.

The best method of diagnosing a Scotland encephalomyelitis is a serological investigation. The patient's blood reveals a high titer of virus-neutralizing and complement-binding antibodies which are preserved for several years.

Bearing in mind that the antigenic structure of the Scotland encephalomyelitis virus is similar to the causative agent of the tick-borne vernal encephalitis, the neutral reactions and complement-fixations should be carried out on a broad scale and always with 2 viruses. It is frequently difficult to differentiate the 2 viruses by their titers in the mentioned reactions; a biological test should be made in such cases.

White and cotton rats are not susceptible to the virus of the tick-borne vernal encephalitis, whereas the Encephalophilus scotticus can be adapted to these animals.

Prophylactic measures and treatment. A formalin-treated vaccine which was successfully used on sheep in Scotland is available for the specific prophylaxis of the disease. The nonspecific prophylactic measures are designed to prevent tick bites.

West Nile Encephalitis

Definition. The West Nile encephalitis or, as it is more frequently called, the West Nile fever, is a benign but acute febrile disease of a viral etiology which can be transmitted to man by mosquito bites.

History. The West Nile fever was quite recently singled out as an independent nosological unit of a group of so-called fevers of unknown origin which are so widespread in the tropical and subtropical areas.

The agent of this disease, unlike those of most of the other infectious diseases, became known considerably earlier than the fever itself. The virus was isolated in Africa in 1940 by Smithburn, Hughes, Burke, and Paul from the blood of a woman suffering from the fever, but they did not succeed in tracing the symptomatology of the disease.

In 1942 Lefcovitch described the clinical picture of a disease of unknown etiology which had occurred in Israel. A comparison of Lofcovitch's data with the subsequent descriptions of the West Nile encephalitis indicates that Lefcovitch had dealt precisely with that disease.

In 1951 Bernkopf, Levine, and Nerson isolated the virus from the blood of patients and described the clinical picture of the disease.

In 1952 Taylor and Halbert isolated the virus of the West Nile fever from mosquitoes caught in Egypt.

Etiology. The causative agent of the West Nile fever is the filtrable virus Neurophilus nili. The sizes of the elementary particles range within 20-20 mμ. The virus passes through the N, V, and W Berkfeld filters and Zeits filters.

The Neurophilus nili is immunologically related to the virus of the St. Louis and Japanese encephalitis, which is shown in both the complement-fixation reaction and neutralization tests (Simburne, 1942; Casals, 1944).

In the external environment the agent is not very stable and rapidly dies at room temperature. At a temperature of 55° the virus-containing material becomes harmless in 30 minutes.

To preserve the strains, it is recommended that they be kept in suspensions of organs of the infected animals in cold air. If kept on ice, the virus can be preserved for at least 2 weeks, and when vacuum-dried it may last many months.

The virus is more stable in the presence of an albumin and it is therefore suggested that a 10% physiologic solution of rabbit or horse serum be used when handling the virus, particularly for the preparations of dilutions.

The virus is easily cultivable on chicken embryos whose yolk sacs have been infected, and on the chorioallantoic membrane on which the infection is revealed in the form of typical patches (Bernkopf, Levine, Nerson, 1953). The maximum virusemia is reached between the second and fourth day, and the embryo dies between the third and fifth day. The embryos are more sensitive to the virus of the West Nile fever than white mice, which prompts certain re searchers to recommend the use of the chorioallantois for virus titration purposes (Watson, 1943).

Tissue cultures of the virus have been prepared from the brain tissue of a mouse embryo, a whole chicken embryo, a chicken embryo without a central nervous system, and a whole mouse embryo. Being cultivated in tissues, the pathogenic properties of the virus may be considerably changed. On the one hand the virus may acquire the capacity to kill the mice even in case of extraneural infection and, on the other, lengthy passages are frequently followed by the complete loss of virulence (Kaprowski, Lennet, 1946).

White mice, hamsters, and rhesus monkeys are susceptible to the virus of the West Nile encephalitis. The usual laboratory model for the isolation of the virus are white mice, which are particularly sensitive to intracerebral infection. The symptoms and histopathology of the brain of these animals are typical for viral encephalitis. The incubation period in case of a cerebral infection lasts on the average from 4 to 5 days, after which the first symptoms of the disease appear. The sick

animals become sluggish, their wool matted, their rear extremities paralyzed. Death usually comes between 12 and 48 hours after the first clinical symptoms appear. Degenerative changes in the Pourkinje cells are found in the brain of the dead animals (Olitsky and Casals, 1952).

The mice are considerably less sensitive to intraperitoneal and subcutaneous infection.

Rabbits, guinea pigs, white and cotton rats are unsusceptible to the virus of the West Nile fever when it is introduced into the cerebrum in very massive doses (1 million mouse doses LD_{50}). After the infection, however, complement-fixation antibodies accumulate to produce a high titer (Davies, Yoshpe-Puper, 1954).

Epidemiology. The epidemiology of the West Nile Fever is still practically unknown, and only individual facts can therefore be discussed.

Cases of the West Nile fever have been recorded in Africa (Egypt, Uganda) and various areas of the coastal area in Israel. It is not impossible, however, that the disease occurs also in other areas. Recent investigations have shown that virus-neutralizing antibodies against the Neurophilus nili are widespread among the population of equatorial Africa and India.

It is worth mentioning that while symptomatic forms of the disease prevail on the African continent, the considerable outbreaks of the fever occurring periodically in Israel are relatively severe.

The reservoir of the virus in nature has not yet been established. It is assumed, by analogy with other viral encephalites, that virds play an important part in this respect (Goldbloom, Sterk and Padyerkiy, 1954).

York, Halbert, and Taylor (1953) succeeded in isolating the virus from the blood of 2 pigeons caught in the endemic area of the Nile delta.

The disease is apparently transmitted through the bites of various types of Culex mosquitoes (Culex antennatus, Culex pipiens, Culex univittatus) whose spontaneous infectivity in Egypt was proved by Taylor and Halbert (1953). The transmission of the West Nile encephalitis virus from sick to healthy mice by the bites of Culex mosquitoes (Culex antennatus, Culex pipiens) can be observed also under laboratory conditions. The mosquitoes are capable of transmitting the agent in 7-20 days after having fed on sick animals.

The possibility of infecting the Aedes aegypti mosquitoes with the virus was proved under laboratory conditions by Goldwasser and Davis (1953) and Davies and Yoshpe-puper (1953). The infected mosquitoes transmitted the virus through their bites to healthy animals throughout their lives. On the basis of these data, the Aedes aegypti mosquitoes are looked upon as only potential carriers, since this type of mosquito very seldom occurs in the endemic areas of the West Nile fever. The West Nile fever is also seasonal: its outbreaks in Israel have always occurred during the last months. The first cases of the disease usually broke out at the end of July, rising to the highest level by the end of August and early September, and showing a sharp decline by the end of September.

No relationship has been established between the incidence of the disease and certain age groups of the patients. The disease affects both children and adults.

The clinical picture. The incubation period of the disease has not been definitely established. Certain researchers believe it is between 2 and 5 days. The disease, as a rule, begins in an acute form and is accompanied by chills, severe frontally-localized headaches, aching pupils, as well as pains in the chest and the waistline and a general weakness.

The temperature rapidly rises to 38-40°, remains at that level for 2-3 days, and lytically returns to the norm in the following 2-3 days. In a number of cases, the temperature is characterized by a 2-hump curve.

An examination of the patient reveals a reddening of the face and conjunctiva, which is one of the characteristic symptoms of the disease. A hyperemia of the pharynx is noted in some patients.

A general enlargement of the lymph nodes is observed. Their diameters vary from 0.5 to 1.5 cm. They are occasionally painful during palpation.

Many patients develop a macula-papular rash all over the body which disappears fairly rapidly.

It is impossible to establish any deviations from the norm on the part of the cardiovascular system with the exception of a more frequent pulse which corresponds to the temperature level.

Pathological symptoms of the respiratory organs are absent.

A disordered gastrointestinal tract is observed in a number of patients: lack of appetite, nausea, and diarrhea. The spleen is somewhat enlarged but not painful.

Mild symptoms of irritation of the cerebral membranes (rigidity of the occipital muscles, the Kernig symptom) frequently occur in the central nervous system. An investigation of the spinal-cord fluid reveals an increase in the quantity of regular blood and albumin elements.

Leucopenia with a relative lymphocytosis is observed in the blood (Bernkopf, Levine, Nerson, 1953; Southam, Moore, 1954; Hamilton, Taylor, 1954).

The prognosis of the West Nile fever is favorable: there is no reference in the literature to lethal cases, complications or afteraffects. Recuperation, however, is slow, usually lasts 1-2 weeks, and is accompanied by general weakness. The enlarged lymph nodes revert to norm within a month or two. The first attack may be followed by relapses with the same but less pronounced clinical symptoms.

COMPARATIVE CHARACTERISTICS OF EPIDEMIC ENCEPHALITIS

Name of disease / Characteristics	American St. Louis encephalitis	American western equine encephalitis	American eastern equine encephalitis
Agent	Filtrable virus, size 20-30 mμ	Filtrable virus, 25-40 mμ	Filtrable virus, 20-30 mμ
Virus reservoir in nature	Finally not established. Birds and small rodents suspected.	Finally not established. Birds and wild animals suspected.	Finally not established. Birds suspected.
Carriers	Culex tarsalis and Culex pipiens mosquitoes and Dermanyssus gallinae ticks of the gamasoidea family.	Culex tarsalis, Aedes dorsalis, Aedes aegypti, and Aedes vexans mosquitoes, and Dermacentor andersoni and Dermacentor variabilis ticks.	Believed to be Aedes sollicitans and Aedes vexans mosquitoes and Dermacentor andersoni ticks.
Transmitting the virus to man	Through mosquito and tick bites	Through mosquito and tick bites	Through mosquito and tick bites
Incubation period	4-21 days	5-10 days	Not determined
Clinical characteristics and prognosis	Rapid development of disease. Particularly severe in children. Recovery is complete in most cases and takes several weeks. The aftereffects in some people are tremors and mental debility.	The clinical picture & prognosis of disease are similar to those of American St. Louis encephalitis.	Very painful course. Acute manifestations lasting 2-3 weeks. 60% recovered patients retain various aftereffects, from emotional instability to paralysis and mental debility.
Mortality	Depends on age: up to 30% among children and 5% among adults	Up to 8% among adults and 20% among children	Reaches 74%

COMPARATIVE CHARACTERISTICS OF EPIDEMIC ENCEPHALITIS

Name of disease / Characteristics	Venezuelan equine encephalomyelitis	Australian encephalitis (X-disease)	Scotland encephalomyelities (louping ill)	West Nile encephalitis
Agent	Filtrable virus	Filtrable virus	Filtrable virus 15-20mμ	Filtrable virus, 20-30mμ
Virus reservoir in nature	Unknown	Unknown	Sheep & possibly wild rodents.	Unknown. Birds suspected.
Carriers	Believed to be Aedes Taeniarhynchus culex mosquito, & Mansonia titillans mosquitoes.	Unknown	Ixodes ricinus and Rhipicephalus appendiculatus ticks.	Culex antennatus, Culex pipiens & Culex univittatus mosquitoes.
Transmitting the virus to man	Through mosquito bites. Possible aerogenic infection presumed (cases of laboratory infection).	Unknown	Through tick bites	Through mosquito bites
Incubation period	Not determined	5-12 days	Not known definitely. Believed to be about two weeks	Not established. Believed to be 2.5 days
Clinical characteristics and prognosis	Disease is relatively mild, lasts 3-5 dys, less frequently 7-8 dys. Recovery, as a rule, rapid and complete.	Very painful course. In lethal cases patients die on 4-5th day. In case of recovery acute symptoms disappear in 10-12 days.	Disease consists of 2 phases lasting a total of 4-5 weeks and ending, as a rule in recovery.	Disease is comparatively mild. No complications or aftereffects observed.
Mortality	Not established. Some lethal cases mentioned.	Reaches 70%	Not established	No lethal cases mentioned

Diagnosis. The lack of specific symptoms makes a clinical diagnosis of the West Nile fever extremely difficult. A final diagnosis can be made only on the basis of a laboratory analysis.

It should be borne in mind that indistinct and asymptomatic forms of the disease are widespread in addition to the clinically pronounced forms. There are known cases of virus-isolation from the blood of clinically healthy people (Melnik, Paul, Riordan, and others, 1951).

Laboratory diagnosis. A laboratory diagnosis is made by isolating the agent from the patient's blood, as well as by a complement-fixation reaction.

The earlier the blood is taken from the patient, the easier it is to isolate the virus. The strains isolated by an intracerebral injection of white mice is further identified by immunological reaction methods (complement-fixation reaction, cross-resistance tests). A 10% emulsion of the brains of the dead animals is used for further passages.

The accumulation of complement-fixation antibodies in the patient's blood occurs only in the recuperation period (by the 15th-20th day after the onset of the disease), and the complement-fixation reaction can therefore be used only for a retrospective diagnosis.

The virus-neutralizing antibodies appear at still later periods. The complement-fixation antibodies are preserved in the blood for 3-4 months, and the virus neutralizing antibodies disappear considerably later.

It should also be borne in mind that in a large number of people in the endemic areas the sera produce a positive reaction.

Treatment. Symptomatic and general tonic therapy are resorted in view of the lack of specific treatment.

Measures against the disease and prophylaxis. No vaccine has been developed against the West Nile fever.

The prophylactic measures against the West Nile fever are limited to the extermination of the carrier mosquitoes and the prevention of their bites.

LYMPHOCYTIC CHORIOMENINGITIS

Definition. Lymphocytic choriomeningitis is an acute viral disease of man and muridae rodents; the latter are the reservoir of this particular virus.

History. Acute serousmeningitis was singled out as an independent nosological unit as early as 1909 by the Kazan' neuropathologist L. O. Darkshevitch. In 1925 Walgren described the first symptom complex of the disease in man which he had singled out as an independent nosological unit called acute aseptic meningitis. It was later established that acute aseptic meningitis was not an independent disease but a combination of symptoms which may have a different etiology and is brought about by the virus of lymphocytic choriomeningitis (Rivers and Scott, 1935). The virus of lymphocytic choriomeningitis was first discovered in monkeys by Armstrong and Lilly in 1934.

Etiology. The causative agent of the disease is a filtrable virus Meningophilus choriomeningitidis.

The size of the virus is 40-60 μ and it can pass through the N, V, and W Berkefeld candles and Zeits filters.

At a temperature of 56° the virus is destroyed in 20 minutes, and at 37° in 1-2 days; it is highly sensitive to soap and penicillin, well preserved under vacuum and cold temperature and rapidly inactivated at room temperature.

Monkeys, mice, field mice, speckled trout, guinea pigs, dogs, cotton rats, and hamsters are susceptible to the virus. Rabbits and birds are unsusceptible. White mice and guinea pigs serve as laboratory models. Intracerebrally infected white mice develop spasms, tremors, and convulsions. Death comes in 1 to 3 days after the onset of the disease. In case of an intranasal infection, the development of the disease in mice is irregular.

Guinea pigs become sick after an intracerebral, parenteral, and intranasal infection and die between the 10th and 12th day.

The virus is found in the blood, brain, spleen, lungs, and urine of both the mice and guinea pigs.

Intracerebrally infected monkeys develop fever, sluggishness, loss of appetite, and hyperasthesia 5 to 14 days after the incubation period. In the case of sick monkeys the virus is found in the brain, blood, internal organs, testicles, bone marrow, and salivary glands (A. K. Shubladze and S. Ya. Gaidamovitch, 1953).

The pathoanatomical changes in the experimental animals are characterized by lymphocytic infiltration in the area of the vascular plexis and in the soft cerebral membrane of the brain stem.

The virus is cultivated on 10-12 day-old chicken embryos; tissue cultures have also been developed. Various virus strains are pathogenically quite different from one another.

V. M. Zhdanov (1953) believes it expedient to divide the virus of the lymphocytic choriomeningitis into 3 different types which are possibly independent types and pathogenic in man:

a) Meningophilus choriomeningitidis var. communis, the most widespread type, is the causative agent of the natural infection of mice;

b) Meningophilus choriomeningitidis var. tchumakovi, is the agent of the psychosensory diseases of children (chorioencephalitis), isolated by Tchumakova and Voroshilova (1947); it is mildly pathogenic in guinea pigs and is immunologically different from the ordinary strains of this virus;

c) Meningophilus choriomeningitidis var. homminis, isolated during the outbreak of neuroinfectious diseases (Verlinde, 1948), pathogenic in guinea pigs and mildly pathogenic in mice.

A number of other diseases are related to lymphocytic choriomeningitis but their natures have not yet been finally established. But the establishment of their etiology is urgently dictated by the considerable resemblance of their clinical picture.

The antigenic structure of the lymphocytic choriomeningitis virus is complicated and has not yet been adequately studied.

Epidemiology. Gray household mice, field mice, forest mice and apparently other murine rodents are the reservoir of the virus. Infected household mice secrete the virus to the end of their life without revealing any visible symptoms of the disease (V. M. Zhdanov, M. E. Levy and N. N. Basov, 1950; L. N. Kislyakova, 1953).

The carriers of the virus are Allodermanyssus sanguineus and Lyponyssus bacoti ticks of the Gamasoidea family. Their capacity for infecting animals during the blood-sucking, their spontaneous infectivity and the possibility of transmitting the virus by ovarian methods, has been convincingly proved.

The ticks investigated in the lymphocytic choriomeningitis areas reveal a certain seasonal numerical increase during the spring-summer period, with the Allodermanyssus sanguineus ticks recording their greatest increase in the summer and the Lyponyssus bacoti in the spring (L. N. Kislyakova, 1953). Spontaneous infectivity has been established also in the Dermacentor andersoni ticks.

It has been suggested that certain types of mosquitoes, fireflies, and lice are the carriers of the lymphocytic choriomeningitis virus (Olitsky and Casals, 1948).

The possibility of infecting fleas with a lymphocytic choriomeningitis virus by feeding them on infected animals during virusemia has been established; but the transmission of the virus through infected fleas from infected to healthy animals has not been recorded (L. N. Kislyakova, 1953).

The disease is characterized by natural foci. The formation of anthropurging sources of infection is also possible in view of the presence of gray household mice in residential, warehouse, and industrial buildings (Zhdanov, 1953).

Man can be infected by mice through the bites of carrier ticks. Other possible sources of infection should not be ruled out.

The mice release the virus with their excrements, urine, and nasal mucus which may contaminate foodstuffs, water, residential places, warehouses, and other buildings. Under certain conditions the dry excretions of the mice turn to dust which contaminates the air. Breathing that air may produce an infection in people (Armstrong, 1941).

A sick person is, to some extent, also dangerous for the surrounding people, as his urine may contain the virus. But the possibility of the patient's excrements containing the choriomeningitis virus is ruled out.

It should be pointed out, however, that it was found impossible under experimental conditions to infect mice with the lymphocytic choriomeningitis virus either by applying the virus to the scarred skin and mucous membrane of the oral cavity or by introducing the virus-containing material into the gastro-intestinal tract. In the absence of ectoparasites, the close and lengthy contact between naturally infected and noninfected mice also failed to produce an infection in the latter (Kislyakova, 1953).

The disease is prevalent everywhere (U.S., England, France, Japan, USSR) and has been described in various countries. The largest number of cases occur in the winter and spring months, which is apparently due to the largest population of murine rodents in residential buildings during that period.

Choriomeningitis mostly affects people between 20 and 30, and men and women are equally susceptible to the disease.

In addition to the clinically pronounced forms of the disease, there are cases when it occurs asymptomatically. In the U.S., for example, an investigation of the serum of 2,000 people who showed no symptoms of the disease revealed neutralizing antibodies in 11% of them (Armstrong, 1941).

The clinical picture. There are several known clinical forms of choriomeningitis: aseptic meningitis, meningo-encephalomyelitis, a grippe-like disease, and an acute general fatal disease.

Meningeal and grippe-like forms account for most of the cases.

The incubation periods lasts 7-13 days.

The disease, as a rule, starts suddenly and reveals symptoms resembling a severe grippe. It is accompanied by severe headaches, nausea, vomiting, a high temperature and confused mind. Angina and catarrhal symptoms are sometimes observed in the respiratory tracts. The patients lose weight. The disease lasts 7-10 days.

In the case of many patients the disease does not progress beyond this point and a rapid recovery follows. In others the grippe phase is followed by a meningeal phase which lasts about 2 weeks and is followed by recovery.

In neurological and general forms of the disease, which are quite rare, the symptoms are quite different and are determined by the degree and locality of the injury in the central nervous system.

A moderate neutrophylic leucocytosis is found in the patient's blood during the fever period. The cerebrospinal fluid is under increased pressure; the quantity of albumin in it is slightly increased; the sugar content is within the norm; a lymphocytic pleocytosis -- from 150-250 to 1,700-33,000 cells per 1 mm^3 -- develops (Olitsky and Casals, 1952).

In the great majority of cases the disease ends in recovery. Published materials contain no reference to mortality produced by lymphocytic chorio-meningitis. Death is caused only by the so-called general forms of the disease.

Pathological anatomy. Inflammatory changes in the soft cerebral membrane, ependyma, and vascular plexus are observed in the neurological forms of the disease. These changes coincide with those usually observed in all cases of viral encephalitis.

Pronounced inflammatory processes in the lungs and liver are noted in the rare cases of the generalized disease (which end in death) (Smadel, 1942).

Diagnosis. The virus can be isolated from the blood and cerebrospinal fluid of the patients.

When a post-mortem diagnosis becomes necessary, small pieces of the cerebrum are used for investigation purposes. The serum can be used 2 weeks after the onset of the disease for a complement-fixation reaction and 1½-2 months for a neutral reaction.

The methods of isolating the virus, as well as the methods of serological investigations, are the same as those used for the virus of the St. Louis encephalitis.

Treatment. It has been suggested that aureomycin and terramycin are effective in the treatment of lymphocytic choriomeningitis (Welch, Levis, Kiefer, 1953).

Prophylaxis. The major prophylactic measures against lymphocytic choriomeningitis are those designed for large-scale extermination of mice.

Sanitary-prophylactic measures designed to protect the houses, warehouses, and other buildings against the penetration of mice should also be carried out.

Every possible measure should be taken to exterminate the ticks and to protect the people from their bites.

All the rat-extermination and disinfestation measures should be carried out according to the commonly accepted methods outlined in the handbooks and instructions on disinfection, disinfestation, and rat extermination.

The patients should be isolated and their excrement and urine disinfected.

There are no specific prophylactic methods against the disease.

THE COLORADO TICK FEVER

History. The first reports of this disease appeared over 100 years ago and were made by doctors working in the Rocky Mountain area. But it was first classified as an independent nosological unit by Becker only in 1930.

In their study of the Colorado tick fever, Topping, Gulliford, and Davis (1940) came to the conclusion that the development of this disease in man was due to the bite of the Dermacentor andersoni tick; this suggestion had been made earlier by Becker. But these researchers were unable to isolate the agent either by infecting experimental animals or by passages on chicken embryos.

The virus was first isolated and investigated by Florio, Stewart, and Muggridge (1944) who succeeded in infecting hamsters by the parenteral introduction of sich animals' blood.

By adapting the virus to the organism of white mice and developing chicken embryos, Koprowskiy and Cox (1946) developed an experimental vaccine.

Etiology. The causative agent of the Colorado tick fever is a filtrable virus polyvectus Colorado measuring 10-12 mμ. The virus passes through the N. V, W Berkefeld candles and Zeits filters and has a pronounced stability. It can last more than 2 months at room temperature and about 3½ years in an ordinary refrigerator. When vacuum-dried it can retain its activity for a particularly long time. A 60° temperature inactivates the virus-containing suspension in 30 minutes. Neutral and complement-fixation reactions were used to prove the immunological difference of the Colorado tick fever virus from those of the dengue fever, tick and Scotland encephalitis from Western and Eastern equine encephalitis, Venezuelan equine encephalitis, St. Louis encephalitis, lymphocytic choriomeningitis, rabies and yellow fever (Koprowskiy and Cox, 1946, 1947; De Boer, Kunts, Koprowskiy, Cox, 1947).

Of the experimental animals, only the hamsters are sensitive to the virus, and they are used as models for isolating and passing the virus. In the first tests on intraperitoneally infected hamsters, the infection appears asymptomatically, but in about the 12th test the hamsters begin to die and eventually their mortality fluctuates from 25 to 50%.

An autopsy of the dead animals reveals changes in the spleen. On the cutoff sections colored with hematoxylin-eosin the changes can be seen as follicles of a degenerative nature. There is a reduction in the number of leucocytes in their central parts and large quantities of pale mononuclear cells mixed with polynuclear leucocytes and erythrocytes appear on the scene. The follicle limit, usually clearly outlinted, appears to be indistinct. When colored by the Romanovskiy-Giemsa method, the large mononuclear cells reveal oesinophilic and

basophilic protoplasmic inclusions (Black, Florio, Stewart, 1947).

The virus can be adapted to the organism of white mice by the intracerebral passage method. Under this method of infection the first symptoms of the disease appear on the 3rd and 4th day: a paralysis of the extremities develops. The animals die between the 5th and 7th day.

Young mice are susceptible also to the intraperitoneal infection with the virus.

The causative agent of the Colorado tick fever can be easily cultivated on developing chicken embryos by infecting their yok sac.

Epidemiology. The Colorado tick fever occurs only in the U.S., where it is prevalent in a number of states, particularly in Colorado, California, Oregon, Montana, Utah, Idaho, Nevada, Washington, and Wyoming (Elkund, Kohls, Brennan, 1955). The tick fever virus was frequently isolated from the Dermacentor variabilis ticks collected in Long Island (N.Y.), but no cases of people contracting the disease in that area have been recorded.

Characteristic of the epidemiology of the described disease is, first of all, the fact that it is closely associated with ticks. Its prevalence is limited to the areas inhabited by ticks. The Colorado fever is usually contracted by persons closely associated with the forest by occupation (shepherds, lumberjacks, etc.). The disease is strictly seasonal: the outbreak of Colorado fever cases coincides with the period of the highest activity of the ticks. In almost all cases the patients' anamnesis reveals indications of their having visited the forest 4-5 days before the onset of the disease, and ticks are found sticking to their body. Investigations carried out by a number of researchers showed that the Dermacentor andersoni tick is the carrier of that virus, and that the female of the species is capable of transmitting the virus to its progeny. These facts prove without a doubt that the infection of man is brought about by the bite of an infected tick and that the Colorado fever is characterized by a natural facus.

Some significance from an epidemiological point of view attaches also to the Dermacentor variabilis and Dermacentor occidentalis ticks from which the virus was isolated; cases of the disease were recorded in their natural habitat.

In addition to the mentioned species, the virus was isolated also from the Dermacentor albopictus ticks in west Montana, Otobius lagophilus ticks in the northern parts of Nevada and Utah, and Dermacentor parumapterus ticks also collected in Nevada (Elkund, Kohls and Brennan, 1955).

The attempts to identify the warm-blooded hosts of the virus have so far been unseccessful.

The clinical picture. The incubation period of the Colorado fever lasts 4-5 days.

The clinical picture is characterized by an acute onset without any previous warning. Chills and aches are felt all over the body, the temperature rises rapidly, reaching 38.9 - 40° and remains at that level for 2-3 days. The dominant symptoms of the fever period are headaches; photophobia; pain in the eyes, waistline, and muscles; and cutaneous hyperasthesia. Noted also is loss of appetite, nausea, and vomiting.

Objective investigations have not succeeded in establishing any deviation from the norm with the exception of an insignificant hyperemia of the conjunctiva and mucous nasal pharynx, as well as a faster pulse beat in keeping with the temperature. A pronounced leucopenia is found in the blood: the number of leucocytes goes up to 2,000 - 3,000 per 1 mm^3.

After 2-3 days the fever is followed by a remission lasting approximately as long. The temperature drops to normal or even subnormal. All the symptoms, with the exception of some weakness, disappear during this period.

The remission is again followed by an attack of fever accompanied by the above-described symptoms. The second attack does not last more than 1-2 days and is then followed by a period of recovery which is fairly long in comparison with the relatively short period of the fever and lasts 5 to 7 days.

In some cases, especially in children, the Colorado fever may be more painful and reveal pronounced symptoms of meningo-encephalitis. But even in these cases the outcome of the disease is favorable. There are no published references to lethal cases or complications.

The disease leaves a stable immunity behind it. There have been no reports of recurrent cases of Colorado fever. Attempts to artificially infect former Colorado fever patients were not successful.

Diagnosis. The diagnosis of Colorado tick fever is based on the typical anamnesis of the patients (a tick bite or a visit to the forest inhabited by ticks), the typical 2-hump temperature curve, and other symptoms peculiar to this disease.

Laboratory diagnosis. To confirm the clinical diagnosis, it is recommended that the virus be isolated from the sick animals by way of an intraperitoneal infection of 3-4 day-old white mice with 0.05 ml of blood serum taken during the attack of the fever. The mice become sick on the 6th-7th day after the infection. The isolated strains are identified by a neutral reaction on young suckling mice with the use of hyper-immune serum introduced intraperitoneally.

Complement-fixation and virus neutralizing reactions which produce fairly accurate results are recommended for a serological diagnosis. But these 2 reactions can be used only at later stages of the disease, as the complement-fixation and virus-neutralizing antibodies appear only in the recovery period, between the 9th and 14th day

after the onset of the disease (Cox, 1952). Antigens prepared from the brain of the infected mice are used for complement-fixation reactions.

Treatment. Inasmuch as no specific methods of treating the disease have been suggested, such treatment must be limited to symptomatic therapy.

Prophylaxis. The specific prophylaxis of the Colorado fever is still in the stage of laboratory experiment. Koprowskiy and Cox (1947) reported the immunization of 20 volunteers with a live virus adapted to a chicken embryo by way of repeated passages. Between the 6th and 7th day after the vaccination, 11 of the 20 volunteers developed a mild disease limited to a single attack. Five of the vaccinated volunteers tested by the introduction of human strains revealed a definite immunity.

Since the disease is transmitted by ticks, individual prophylactic measures consist in the protection against their bites when visiting an endemic area.

THE HEMORRHAGIC FEVER GROUP

In the past 10-20 years Soviet scientists have discovered and studied a number of endemic viral diseases, combining them into a hemorrhagic fever group on the basis of their common etiological, epidemiological, pathogenic, and clinical features.

Three different types of hemorrhagic fever are currently known (M. P. Tchumakov): the Omsk hemorrhagic fever, the Crimean hemorrhagic fever (and the Central Asiatic and Bulgarian fever related to it), and the hemorrhagic nephrosonephritis (hemorrhagic fever with the kidney syndrome).

But despite their considerable similarity, each of the 3 mentioned diseases has a specific causative agent, a definite reservoir of the virus and method of transmitting it, its own endemic source and clinical characteristics, which made it possible to classify these diseases as independent nosological forms.

These diseases, combined into a hemorrhagic fever group, also have a number of common features with certain other endemic diseases: yellow fever, dengue fever, Pappataci fever, Colorado tick fever, and certain other clinical forms of tick encephalitis.

Omsk Hemorrhagic Fever

Definition. The Omsk hemorrhagic fever is an acute febrile disease of a viral etiology characterized by a hemorrhagic syndrome: it occurs in the Omsk and Novosibirsk oblasts and is transmitted by ticks.

History. It is impossible to establish the exact time when the first cases of the hemorrhagic fever occurred in the Omsk oblast. They had apparently appeared long before the period when the first cases of the "obscure disease" were recorded. Back in 1940, B. P. Pervushin observed certain diseases that did not fit into the clinical picture of the known acute infections and had earlier been diagnosed as atypical cases of grippe, typhus, malaria, tularemia, and other infectious diseases. The local physicians pointed out that the "new disease" originated in 1940 and associated it with the muskrats inhabiting the lakes (N. M. Tatarintsev); but the role of the muskrat in the epidemiology of the Omsk hemorrhagic fever is still not clear.

A systematic study of this disease was begun in 1946 by an expedition organized by the Omsk department of the public health service under the leadership of R. M. Akhrem-Akhremovitch and G. I. Netskiy. It was established that the disease was not contagious and effects exclusively the rural population connected with field work; the highest incidence of the disease occurs in the spring and autumn months. At the same time, A. V. Fedushin and G. I. Netskiy established that the incidence curve of the Omsk hemorrhagic fever coincides with the

period the cattle is attacked by the Dermacentor pictus imodic tick. This led to the conclusion that the Dermacentor pictus was the most probably carrier of the causative agent.

Two complex expeditions of the Academy of Medical Sciences USSR headed by M. Tchumakov and including a number of clinical physicians were carried out in Omsk oblast in 1947 and 1948.

It was established that the causative agent of the disease was a filtrable virus always found in human blood in the first 5 days following the onset of the disease.

In 1947 the virus of the Omsk hemorrhagic fever was isolated a number of times by M. P. Tchumakov, A. V. Gagarina, A. P. Belyayeva, and N. S. Slavina from the blood of human patients and suspensions of powdered Dermacentor pictus adult ticks collected in the endemic areas of the Omsk oblast. It was further established that the virus was kept in the ticks during the inter-epidemic period and is also transmitted ovarially by the ticks to their progeny. These data made it possible to consider the carrier tick as the reservoir of the virus in nature.

The clinical and laboratory features of the disease were eventually established and prophylactic and therapeutic methods developed (M. P. Tchumakov, R. M. Akhrem-Akhremovitch, G. A. Sizemova and E. I. S. Novitskiy, etc.).

Etiology. The etiology of the Omsk hemorrhagic fever was established in 1947 by M. P. Tchumakov, A. P. Belyayeva, A. V. Gagarina, and N. S. Slavina. The causative agent of the Omsk hemorrhagic disease is a filtrable virus Hemorrhagogenes sibiricus regularly found in the blood of fever patients as well as in naturally infected ticks.

The virus of the Omsk hemorrhagic fever, just like those of the other types of hemorrhagic fever, can easily pass through filters which cannot be passed by bacteria (Zeits, V and N Berkefeld candles and Chamberlin L5); regardless of the method of cultivation, the virus does not form any elementary corpuscles visible through an optical microscope.

The virus is not very resistant to the effect of various chemical and physical factors. It is resistant to glycerin, capable of lasting a long time (about 2 years) in vacuum-dried form, and is quite resistant to cold. At the same time, at a temperature of 37° the virus is half inactivated within 6 hours; by heating a virus emulsion to 56° it is completely inactivated in 30 minutes, and to 70° in 10 minutes.

The virus is easily cultivated on 7-day-old chicken embryos, accumulating inconsiderable quantities. Compared to the virus of the Crimean hemorrhagic fever, it has a higher degree of pathogenicity for a larger number of animals (monkeys, calves, guinea pigs, cats, field mice, hamsters, gophers, certain types of birds, etc.) and can be easily adapted to white mice in whose brains it accumulates in

large concentrations (up to 10^{-7} - 10^{-9} minimum lethal doses of 0.033 mm^3).

Introduced into the cerebrum of white mice for a number of consecutive times, the virus manifests its neurotropic properties and a sharp increase in its virulence resulting in 100% incidence among the white mice regardless of the method of infection.

Tested on mice, the virus does not lose its capacity for producing a clinical picture in man typical of the Omsk hemorrhagic fever; that was ascertained through an accidental laboratory infection. The virus adapts itself also to guinea pigs.

Adaptation tests made on white mice and rabbits produced negative or unconvincing results.

Special tests have established the absence of a cross immunity between the virus of the Omsk hemorrhagic fever and the agent of the Crimean hemorrhagic fever and the hemorrhagic nephrosonephritis, thereby establishing the etiological independence of the Omsk hemorrhagic fever. Available data (N. I. Zeytlenok and A. P. Belyayeva) also point to the possibility of an etiological connection between these diseases and the hemorrhagic fever in Bukovina.

Epidemiology. Characteristic of the Omsk hemorrhagic fever is its natural source of infection; it is also a strictly endemic disease in the rural areas of the Bol'shaya Barabinskaya steppe in Omsk and Novosibirsk oblasts. Recent indications point to the presence of a similar or identical disease in the steppe areas of the neighboring North Kazakhstan oblast and possibly also in the virgin lands of Chkalov oblast (M. P. Tchumakov, 1954).

The Omsk hemorrhagic fever is a tick infection. Investigations carried out by Soviet scientists established that the carriers of the causative agent of this disease are the Dermacentor pictus and Dermacentor marginatus ixodic ticks inhabiting the forest-steppe belt of Western Siberia and certain other oblasts. The only known source of infection in man under natural conditions so far has been the bite of an infected tick. It has been proved that under natural conditions these ticks can be infected with the virus, can pass it on to their progeny, and also keep the infection during the inter-epidemic period (winter). Consequently in the case of the Omsk hemorrhagic fever the carrier ticks are simultaneously the reservoir of the virus in nature (M. P. Tchumakov, A. V. Gagarina, N. S. Slavina, A. D. Lebedev, A. A. Avakyan, A. V. Fedushin, and G. I. Netskiy).

Susceptible to the virus are certain types of rodents (young hamsters, gophers, hedgehogs, and field mice), domestic animals (calves and lambs), and birds (crows, rooks and bitterns) which may serve as potential temporary reservoirs of the virus during the acute diseases in the virusemia period. But these animals have not been seen to carry the virus for a long time, and that brings up the problem of the epidemiological significance of the tick as a natural reservoir of the virus (A. V. Gagarina and others). The Dermacentor

pictus and Dermacentor marginatus ticks feed on the blood of warm-blooded animals. The tick goes through 3 metamorphic stages: larve, nympha, and imago. The larvae and nymphae parasitize small animals and birds, while the adult ticks attack large animals (cattle) and man. The adult ticks are naturally most responsible for the spread of the Omsk hemorrhagic fever.

The ticks hibernate in the adult stage. They become active with the rising temperature in the early spring and from the middle of April on attack people and animals. Their greatest activity is in May.

The intensity of the tick attacks on cattle and the likelihood of their attacking people are considerably reduced in the summer months in view of the egg-laying season of the female ticks, as well as the biological characteristics of the newborn larva and nymphae which parasitize small rodents and birds.

In the fall, when the nymphae are transformed into adult ticks, the attacks are resumed, reaching a maximum in September but not approaching the spring level. In the late autumn and winter months the ticks are in a state of diapause.

Thus the curve representing the tick attacks on cattle and people shows 2 rises, a higher one in the spring and a lower one in the autumn.

Inasmuch as the Omsk hemorrhagic fever is transmitted only by the bites of carrier ticks which are also the reservoir of the virus in nature, it is only natural that the epidemiology of the disease should, to a considerable extent, be determined by the ecology and biology of ticks.

The Omsk hemorrhagic fever is strictly endemic to the rural forest-steppe areas of the Omsk, Novosibirsk, and other oblasts where the Dermacentor pictus and Dermacentor marginatus ticks are widespread.

The people usually affected by the disease are those working in the fields in the spring-summer-autumn months, coming in contact with the cattle and attacked by the ticks. The outbreak of the disease frequently extends also to considerable groups of people engaged in agricultural work. Under natural conditions the disease is characterized by a complete lack of contagiosity among people and a definite connection with tick bites. In some cases it was difficult to rule out the possibility of the infection being transmitted by the alimentary method (M. P. Tchumakov); cases of people handling the live virus and being infected by the dust and drops were observed under laboratory conditions.

The disease is definitely seasonal in nature, the maximum incidence occurring in the spring (April-May) and autumn (September-October) months, a lower incidence in the summer and complete absence of the disease in winter. The incidence curve is almost parallel to the one representing the attack on cattle by carrier ticks but runs 1-2 weeks behind it (the incubation period).

All ages can be affected by the Omsk hemorrhagic fever, but most of the people suffering from that disease in 1945-1948 were of a younger age group (10-20 years), with women predominating.

The recovered patients acquire a stable immunity; the disease does not, as a rule, recur.

Pathogenesis and pathological anatomy. The virus of the Omsk hemorrhagic fever enters the human organism through the bite of an infected tick. The virus is found in the blood of the patients from the very beginning of the fever period, that is, 2-7 days after infection. Virusemia remains throughout the entire fever period of the disease (5-15 days) and is occasionally observed also in the first 2-3 days after the temperature drops to normal (M. P. Tchumakov).

According to I. S. Novitskiy, an acute toxicosis resulting in a serious affection of the vessels and vegetative nervous system lies at the basis of the pathogenesis of the Omsk hemorrhagic fever. The most important symptoms of the disease are determined by the affection of the nervous system and vessels; a very pronounced painful syndrome and hemorrhagic diathesis manifested in the form of hemorrhagic rash, bleeding, hemorrhagic infiltration, as well as small and large hemorrhage foci in various organs and tissues.

The changes of the vessels which play an important part in the pathogenesis of the disease are apparently determined by the combined action upon the organism by various pathological mechanisms, of which the following are the most important:

1) the disruption of the neurohumoral regulation of the vascular tonus arising in connection with the affection of the vegetative nervous system and certain ductless glands, particularly the adrenal glands;

2) the immediate action upon the vascular wall by the virus circulating in the blood which is vasotropic and neurotropic;

3) the influence of the toxic and fermentative substances forming in the organism during the decay of the cellular elements.

All these mechanisms affect the permeability of the vascular-endothelial area to a considerable extent. In aggravated cases the result is the destruction of the capillaries, a diapedesis of the erythrocytes, the outflow of the blood plasma from the vessels, the saturation of the interstitial tissue with albuminous fluid, the coagulation of the blood, and disruption of the gas exchange (B. N. Mogil'nitskiy, A. I. Smirnov-Zamkov).

A high degree of generalized intoxication and growing hypoxemia is presumed to play an important part in the pathogenesis of the Omsk hemorrhagic fever and to serve as the cause of such a pronounced degeneration of the nerve cells and parenchymatous elements of the internal organs. The pathoanatomical changes occurring during the Omsk hemorrhagic fever affect all the organs and systems, with a vascular and nervous pathology predominating. Morphologically this is

manifested as a swelling and destruction of the capillaries, serous edema, and diapedic hemorrhages. An edema and a destruction of certain cells, and the formation of lymphoid elements around the brain vessels changed by inflammation, are observed in the nervous system; submiliary necrosis and focal proliferation of the glia cells are revealed.

Degenerative changes with an alternative component predominating are observed in the parenchymatous organs (liver, kidneys, lungs, spleen, etc.). The exudation appears in the form of tissue infiltration with albuminous fluid and erythrocytes (serous and hemorrhagic apoplexia); the migration of the leucocytes beyond the vascular wall is not very pronounced. A hyperplasia of the lymphoblastic and reticular elements is found in the blood-making organs (lymph nodes, bone marrow, spleen).

The clinical picture. The incubation period of the Omsk hemorrhagic fever is not long, fluctuating from 2 to 7 days.

The clinical symptoms of the disease are frequently preceeded by a prodromal period lasting about 6-12 hours and manifested in sluggishness, general weakness, poor appetite, and moderate headaches.

At the onset the disease is, as a rule, acute. The temperature accompanied by chills rises to 39-40° and remains at that level for 5 to 15 days; during that period the temperature is steady or remittent and then begins to drop. A second wave of fever, usually shorter than the first one, is observed in about 40-50% of the cases after the temperature has dropped to a normal or subfebrile level.

The initial period of the disease lasting 3-4 days until the appearance of a rash and other symptoms of hemorrhagic diathesis, is characterized by a high temperature and general toxis symptoms. The patient's complaint of severe headaches and muscular pain, weakness, sluggishness, and lack of appetite are similar to those frequently heard of in cases of other febrile diseases.

The objective investigations carried out during this period do not reveal to the physician any clear-cut pathogenic symptoms. But the combination of symptoms manifested in this disease represent a pathological symptom complex typical of the initial period of the Omsk hemorrhagic fever.

The patients are, as a rule, sluggish and apathetic. An external examination in the very first days of the disease reveals a hyperemia and puffiness of the face, a skin hyperemia on the neck and upper part of the body, an injection /sic/ of the sclera vessels, and a hperemia of the eyelid mucosa. The pharynx is also clearly hyperemic ("a flaming pharynx" -- R. A. Akhrem-Akhremovitch); an enanthema occasionally observed in the pharynx is an analogue of the hemorrhagic rash breaking out in the critical stage of the disease.

Except for the tendency to a relative bradycardia observed in most of the patients, no pronounced changes can be found in the internal organs during that period.

A clinical analysis of the peripheral blood, however, may produce typical results even in that period. A leucopenia with a moderate neutrophilia and a nuclear shift to the left, as well as a mild thrombopenia, gradually develop in the blood from the very first days of the disease. There is a slight increase in the number of erythrocytes and hemoglobin in the red blood with the number of reticulocytes remaining normal.

Thus the initial period of the disease is characterized by a whole number of pathological symptoms which in combination with the appropriate epidemiological symptoms provide the major prerequisites for an early diagnosis of the Omsk hemorrhagic fever. Such symptoms are: an acute onset with a high temperature, generalized toxic manifestations and a severe headache, hyperemia of the skin of the face and upper half of the body, hyperemia of the pharynx with an occasionally pronounced enanthema, and a characteristic picture of the blood.

The critical stage of the disease begins with the appearance of symptoms of a hemorrhagic diathesis (the 3rd or 4th day) and continues until they take an opposite course. Inasmuch as the fever period fluctuates from 5 to 15 days, the critical stage of a short-course fever may extend also to the post-febrile period, that is, the progressive development of painful symptoms in a number of cases may occur after the temperature has dropped. From this it does not follow that the drop of temperature to normal in the Omsk hemorrhagic fever does not indicate the beginning of recovery.

The rash breaking out on the 3rd-4th day of the disease is one of the characteristic clinical symptoms marking the beginning of the critical period. The rash is usually not heavy, it has a slight discharge and is petechial and, less frequently, roseolic. Numerous linear discharges into the skin are observed in some cases (N. M. Tatarintsev). The symptoms of constriction and pinching are usually found to be positive.

Other symptoms of a hemorrhagic diathesis such as nasal, gastrointestinal, pulmonary, and uterine hemorrhages develop simultaneously with the rash of a little later; they are usually recurrent but, compared to other types of hemorrhagic fever, are not heavy and not very dangerous to the life of the patient.

By this time the patient feels considerably worse. The continuing severe headaches are accompanied by an increasing weakness and a complete loss of appetite. A sensation of dryness develops in the mouth and pains appear in the neural stems and muscles.

The patients become still more sluggish and weak. The puffed-up face observed at the beginning of the disease gradually disappears, the hyperemia of the skin is replaced by a pallor against which a cyanosis of the lips, the tip of the nose, fingers, and, sometimes, toes become clearly outlined. There are some indications of a generalized enlargement of the lymph nodes during that period. Investigations of the cardiovascular system (M. E. Kurmayeva and G. A. Sizemova) point to

a relative bradycardia typical of most cases of the disease. The patient's pulse is quite soft and dicrotism is sometimes observed; an extrasystole is seldom noted.

A physical and X-ray examination of the heart reveals that it has been enlarged by 1.5-2 cm, mostly on the left side toward the left ventricle. The heart tones in the critical period, as well as during the lengthy recovery, remain dull.

Electrocardiograms taken of 19 patients (M. E. Kurmayeva and G. A. Sizemova) revealed a reduced voltage in the P, R and T waves in all cases. More than a third of the patients revealed a steep Q_3 wave without any predominant symptoms of different ventricles or the shifting of the S-T_3 intervals above or below the isoelectric line. Moreover, some of the patients revealed a P-Q interval equal to 0.20 seconds and a QRS complex equal to 0.1 second.

A pronounced hypotonia is observed in the arterial pressure from the first days to the end of the disease. The maximum pressure fluctuates between 80 and 90 mm, and the minimum pressure is reduced to 30-50 mm.

Capillaroscopic investigations also indicate an affection of the vessels. According to M. E. Kurmayeva and G. A. Sizemova, a pale rose and sometimes red cappillaroscopic background is noted during the fever period; the protruding separate capillary loops are elongated (the average length of the arterial branch is 190 // and of the venous branch 311 //), and widened, particularly the transitory part of the venous branch. The blood current is homogenous or macrogranular; the sub-capillary rete is sometimes protruding. The turbidity of the capillaroscopic area disappears several days after the onset of the disease. The number of visible capillaries in one linear millimeter increases from 12 to 15 loops. These changes remain also during the recovery period; the same period marks the appearance of auto-anastomoses (a productive reaction on the part of the vascular endothelium).

The venous pressure remains within the norm only during the first days of the disease. Eventually it gradually rises from 95 to 150 mm of the acqueous column, fluctuating within that range for a long time and dropping to normal only during the recovery period.

The circulating blood mass shows a considerable increase during the fever period (there is an average of 100 to 135 ml of blood per kilogram of weight); it drops back to the norm during the convalescent period.

The fluctuations of the blood-flow speed throughout the disease do not exceed 15 seconds.

According to the conclusion reached by M. E. Kurmayeva and G. A. Sizemova, all the branches of the cardiovascular system are affected by the Omsk hemorrhagic fever, but the insufficiency of the blood circulation is moderate. In some cases it is brought about by the more serious affection of the heart and in others by the vasoular system and its nerve regulating apparatus.

The Omsk hemorrhagic fever frequently affects the respiratory organs. Bronchitis is a common phenomenon in this disease. Moreover, according to N. M. Tatarintsev (1949, 1952), almost one third of Omsk hemorrhagic fever patients develop pneumonia. Pneumonia is noted in various age groups (from 7 to 62 years), and in most cases the right lung is affected.

In the majority of cases pneumonia sets in at the very beginning of the disease, frequently between the 3rd and the 5th day, its course is atypical, and its clinical X-ray changes fall into the category of viral pneumonia (R. M. Akhrem-Akhremovitch, N. M. Tatarintsev). Its clinical manifestations are not very distinct. Usually there is no coughing, the sputum is secreted in insignificant quantities, and chest pains, as well as symptoms of pleuritis, are seldom noted. Typical of most cases are weakly pronounced percussive and auscultative data characteristic of the inflammation process in the lungs. The principal clinical symptoms used as a basis for diagnosing atypical pneumonia is sonorous microbacicular rale on a limited area of the lung, a deterioration of the patient's general condition, and the development of dyspnea. Characteristic also is the fact that the development of pneumonia in cases of Omsk hemorrhagic fever is not accompanied by a leucocytosis in the blood and does not produce a pronounced X-ray picture.

In a minority of patients pneumonia develops at a later period, it is not clinically different from the usual focal pneumonia of a bacterial etiology, and is looked upon as a complication of the Omsk hemorrhagic fever.

The development of pneumonia as a rule considerably complicates the course of the disease. Under favorable conditions the inflammatory changes in the lungs disappear in 1 to 2 weeks. But there are also serious cases when pneumonia lasts 1½ to 2 months.

Changes in the kidneys, according to R. M. Akhrem-Akhremovitch, are observed in 20% of the cases. They occur between the 5th and 10th days of the disease and represent a picture of infectious-toxic nephropathy. There is a moderate albuminuria and hematuria and the albumin content in the urine does not exceed 3.5‰. Hyaline and granular cylinders are found in the sediment. "Fibrinous" cylinders and accumulations of vacuolized cells typical of hemorrhagic nephrosonephritis are not observed. The affection of the kidneys is not accompanied by a disruption of their functions, the process does not develop into a chronic stage, and 20-30 days after the onset of the disease, all the changes in the kidneys disappear without a trace.

Considerable changes are noted in the nervous system during the critical stage with the painful syndrome becoming very prominent. According V. A. Zudov, all the patients suffer from severe headaches and most of them complain of pain in the hands, in the waistline, and along the nerves in the stomach. A characteristic symptom is a sharp adynamia of the patients. A considerable number of the patients reveal meningeal symptoms (the Kernig symptom in 23% of the patients

and a rigidity of the occipital muscles in 40%). The functions of the vegetative nervous system, as well as the sense organs, are disrupted comparatively frequently (defective hearing, a perverted taste). Pathological changes in the nervous system are observed both during the fever and sometime after the temperature has dropped to normal

The peripheral blood picture during the critical stage is quite typical. The increased number of erythrocytes and hemoglobins accompanied by a normal or reduced number of reticulocytes, observable at the beginning of the fever period, is replaced by a tendency to anemia by the end of the fever period.

Leucopenia with a moderate neurophilia and a nuclear shift to the left, as well as a moderate thrombopenia, are constantly observed in the leucocytes. Monocytosis, plasmocytosis, and aneoxenophilia are revealed less often.

In the opinion of R. M. Akhrem-Akhremovitch, a hemogram of the Omsk hemorrhagic fever reflects the course of a painful process. The seriousness of the infection is indicated in particular by a pronounced neutrophilia, as well as by a high content of monocytes.

The bone marrow analyzed during the fever by the M. I. Arinkin method is, as a rule, promyelocytic-myelocytic in nature. The erythropoeisis and thrombopoeisis are inhibited and the number of cells of the bone-marrow reticular tissue is increased.

A biochemical test of the blood reveals hypoproteinemia, a moderate ezotemia, and the retention of sodium chloride in the tissues.

Thus the critical stage is characterized by the following major clear-cut clinical symptoms:

1) pronounced symptoms of toxicosis and a high temperature which in some cases is reduced by the end of the first week of the disease;
2) a unique rash and symptoms of hemorrhagic diathesis;
3) a frequent lung affection in the form of atypical pneumonia;
4) changes in the kidneys;
5) frequent changes observable in the nervous system (algesic syndrom, meningeal symptoms);
6) a characteristic picture of the blood.

The recovery period following the Omsk hemorrhagic fever has not been adequately studied or dealt with in our literature.

The symptoms of impending recovery are a normal temperature, improving condition and reqppearance of an appetite, fewer symptoms of intoxication, as well as a reversed development of the symptoms of hemorrhagic diathesis, and changes in the lungs, kidneys, nervous system, and blood-making organs. The lymphocytosis which appears in the peripheral blood is an index of the coming recovery. The convalescence is characterized by a lengthy and extremely slow restoration of the capacity to work, which is due to the lengthy functional deficiency of the organs and systems affected by the disease.

For several weeks the convalescence reveal arterial hypotonia, an enlarged heart, muted tones, as well as electrocardiographic changes.

A functional test including squatting reveals a considerable increase in pulse frequency including a reduced arterial pressure (maximum and minimum) which return to their normal levels only 6-7 minutes later (a normal equals 4 minutes). A Shtange-Gench test shows that the respiration stoppage does not exceed 10-18 seconds (M. E. Kurmayeva and G. A. Sizemova).

The changes in the kidneys reveal a development in the opposite direction only 20-30 days after the onset of the disease; leucopenia may be observed in the blood of the convalescents for a similar period of time.

In 40-50% of the patients the convalescence may be disrupted by a recurrent fever-wave lasting 3-7 days; the second wave is accompanied by the development of general toxic phenomena but is, as a rule, milder than the first.

Prognosis. In the majority of cases the prognosis of the Omsk hemorrhagic fever is favorable. Mortality amounts to about 1% (R. A. Akhrem-Akhremovitch). The disease is followed by a lengthy loss of capacity to work during the recovery period.

Diagnosis. A differential diagnosis must, first of all, rule out grippe, typhus, dengue, yellow fever, Pappataci fever, as well as such infectious diseases as scurvy, the Schonlein-Henoch disease, and elementary toxic aleukia.

The Omsk disease is singled out as an independent type of hemorrhagic fever not only by the characteristics of the causative agent and epidemiology but also on the basis of the unique clinical picture.

Omsk hemorrhagic fever differs from the Chrimean hemorrhagic fever by its midder course, less pronounced hemorrhagic syndrome (light rash, etc.), low sence of anemia and pronounced thrombopenia). Moreover, unlike the Crimean hemorrhagic fever, this disease is characterized by a frequent affection of the lungs (pneumonia in the case of one third of the patients), a recurrent fever wave in a considerable number of patients, as well as several more pronounced changes in the kidneys.

The principal difference between the Omsk hemorrhagic fever and the hemorrhagic nephrosonephritis is in the mild course of the disease, the absence of a characteristic syndrome accompanied by the disruption of kidney functions, and the development of uremic phenomena.

Laboratory diagnosis. The fever period of the Omsk hemorrhagic fever is usually accompanied by virusemia. Complement-fixation and virus neutralizing antibodies are constantly found in the blood of the patients and convalescents.

A laboratory diagnosis is made with the aid of a complement-fixation reaction, a virus-neutralizing reaction, as well as by isolating the agent from the patient's blood.

Of practical significance in the clinical picture is only the complement-fixation reaction, which is used for finding antibodies in the blood of the patients and convalescents and produces positive results after the end of the first week; it is desirable in this connection to investigate the fresh serum at intervals of about 5-10 days. The reaction may be used for retrospective analysis during the recovery period and later.

Available data speak of the successful use of the complement-fixation reaction (in cold atmosphere) for the purpose of finding antibodies in the patient's blood during the first 5 days of the fever.

Neutral reactions are used only for a retrospective diagnosis between the 30th and 40th day after the onset of the disease and for a period of at least 3 years.

It is not difficult to isolate the virus from the patient's blood between the first and fifth day of the disease; it can be achieved by an intracerebral infection of white mice.

The virus multiplies very rapidly in the brain of mice developing symptoms of meningoencephalitis and a paralysis of the extremities and spasms.

Treatment. An effective specific method of treating severe cases of the Omsk hemorrhagic fever is the use of the serum of convalescing patients (M. P. Tchumakov). The blood is taken from a recovering patient between the 40th and 50th day after the onset of the disease and the serum is introduced intramuscularly in 20 ml doses for 3 successive days. This method of therapy has not become widespread in view of the impossibility of obtaining the serum of former patients on a mass scale.

The treatment of the Omsk hemorrhagic fever is, as a rule, symptomatic in nature and designed to weaken the toxicosis and hemorrhagic occurrences. The principal measures consist in early hospitalization of the patients, good care, a large intake of liquids, and symptomatic medical therapy.

The intravenous introduction of ascorbic acid, a 10% solution of sodium chloride, and the injection of vitamin K are the recommended measures for fighting hemorrhagic diathesis.

Pyramidon and phenacetin should be used in case of chills, high temperature, and severe headaches; acute pains may require the use of pantopon and promedole. An intravenous injection of a 40% glucose solution combined with a subcutaneous introduction of insulin is recommended for reducing the autointoxication. Ordinary doses of caffeine and camphor are suggested for stimulating the activity of the cardiovascular system.

Penicilin and sulfa drugs are used for the treatment of pneumonia which complicates the Omsk hemorrhagic fever.

Despite the end of the fever, the patients should be confined to bed for 7-14 days in view of the possibliity of a relapse. Leaving the bed and checking out of the hospital prematurely may prolong the recovery period.

Prophylaxis. The prophylactic measures against the Omsk hemorrhagic fever are designed for:

1) fighting ticks;
2) the active immunization of the population.

The fight against ticks consists in 1) the protection of the person against tick bites and 2) the extermination of the ticks in nature.

The fight against tick attacks on cattle (the treatment of the cattle with creolin) is very important. The ticks can be exterminated by treating the locality with DDT and hexachlorane. A mixture of lysol (5%), naphtha lysol (10%), and phenol (2%) may be used for that same purpose.

It should be borne in mind that the ticks are comparatively resistant to insecticide and may be still alive a day or two after the use of these compounds. But the ticks' capacity for biting is considerably reduced under the effect of insecticide.

The population of the particular areas of infection should be actively immunized against the Omsk hemorrhagic fever with the vaccine developed by M. P. Tchumakov and his colleagues. The vaccine is a formalin-treated 5% emulsion prepared from the brain of white mice infected with the virus of the Omsk hemorrhagic fever. The vaccination is repeated twice subcutaneously; 3 ml are used in the first vaccination and 5 ml in the second.

Experimental investigations point to the high prophylactic activity of the proposed vaccine.

The epidemiological investigations carried out in 1948 in Omsk oblast, involving 12,500 vaccinated and 8,500 unvaccinated people, also showed that the vaccine was harmless and highly effective. In most cases the vaccination produced no pronounced reaction, was easily tolerated by the subjects, and did not involve any loss of working capacity. Of the total number of vaccinated only 3 people, immunized once, and one person immunized twice, became ill. A considerable number of the unvaccinated people were affected by the disease (M. P. Tchumakov, M. V. Los', G. Ya. Schwabauer, M. T. Scheiman). Analogical and very favorable results, showing the prophylactic effectiveness of the vaccine, were observed during the vaccination and revaccination period of 1949-1953.

Crimean Hemorrhagic Fever

Definition. The Crimean hemorrhagic fever is an acute febrile disease of a viral etiology; it occurs in the natural habitat of the Hyalomma plumbeum ticks (in the Crimean steppe, Central Asiatic republics, etc.), is transmitted by bicks, and characterized by hemorrhagic syndromes, symptoms of intoxication, as well as peculiar changes in the blood and nervous system.

History. One hundred and sixty-eight cases of febrile diseases accompanied by hemorrhagic diathesis, as well as by the affection of the hemopoietic apparatus and the nervous system, were recorded in the summer of 1944 in the steppe areas of the Crimea among the population engaged in harvesting. In the spring-summer periods of 1945 and 1946 that disease again broke out in the same areas. The first cases of that peculiar fever were wrongly diagnosed by the physicians as anthrax, sepsis, Pappataci fever, a hemorrhagic form of grippe, malaria, exanthematis fever, enteric fever, etc.

Systematic study of the new disease was begun in 1944 by a group of army physicians (I. S. Drobinskiy, A. A. Kolachev). In the summer of the same year a special expedition of the Academy of Medical Sciences USSR headed by M. P. Tchumakov joined in the effort; after a 3-year study they produced an accurate description of the new disease which came to be known as the Crimean hemorrhagic fever.

The etiological independence and clinical-morphological uniqueness of the Crimean hemorrhagic fever were established in 1944, and the assumption was made that it was transmitted by a tick. The viral etiology of the disease and its transmission by the bites of the Hyaloma plumbeum tick was experimentally proven in 1945 (by the second expedition of the Academy of Medical Sciences USSR). The virus was finally isolated from the blood of the patient and the organism of the carrier (M. P. Chumakov and associates). A thorough study of the characteristics of the causative agent and the epidemiology of the crimean hemorrhagic fever was eventually made, the characteristic features of the pathological anatomy and clinical picture of that disease established, methods of a bacterialogical diagnosis developed, the prophylactic bases studied and specific therapy proposed (M. P. Chumakov).

Etiology. The causative agent of the Crimean hemorrhagic fever is a filtrable virus, Haemorragogenes tchumakovi, whose morphology has not yet been studied. It easily passes through bacterial filters (Zeits "SF" asbestos filter, V and N Berkefeld candles and Chamberlin filters), it is highly resistant to glycerin, can be preserved for a long time (up to 2 years) in powdered form under vacuum, and does not form any elementary corpuscles that can be visible through an optical microscope. The virus can be completely inactivated, retaining its immunogenic properties, under a prolonged effect of warm air (room temperature).

The methods of cultivating the agent of the Crimean hemorrhagic fever, unlike the virus of the Omsk hemorrhagic fever, have not been adequately developed. According to M. P. Chumakov's data, the experiments in cultivating the virus on living chicken embryos and embryonic tissues (chicken and mice) in vitro have so far failed to produce any reliable results and call for further improvement. The disease can be reproduced experimentally only by infecting a limited number of different types of animals. Monkeys, cats, young rabbits, and possibly mice are susceptible to the infection and in some case reveal a typical clinical picture. But even these animals are not uniformly affected by the disease and frequently tolerate the infection without symptoms, which makes it impossible to maintain the virus stems in them systematically. Thus it may be assumed that only man is completely susceptible to the virus of the Crimean hemorrhagic fever (M. P. Chumakov).

Epidemiology. Crimean hemorrhagic fever is a disease stemming from a definite natural focus; considerable outbreaks of this disease were noted in 1944-1946 in the Crimean-steppe areas. Isolated cases of the disease occurred also in the nearby areas (the Kerch and Taman peninsula, Izmail and Kherson oblasts, Moldavian SSR).

Outbreaks of a disease similar to the Crimean hemorrhagic fever have in recent years been noted in the Burgas, Plovdiv, and other districts of Bulgaria (M. P. Chumakov, 1954). Available information tells of isolated cases of that disease occurring also in the Volga delta and in rayons of the Astrakhan oblast (N. A. Zeitlenok, K. Vanag, 1955, quoted by Chumakov, 1954).

Bearing in mind that the hemorrhagic fever in the Uzbek and other Central Asiatic republics can be classified with a high degree of probability as the Crimean hemorrhagic fever (M. P. Chumakov, 1954), the large geographic area of the natural sources of that infection becomes obvious.

The disease is part of a group of transmissive diseases; its carrier is the Hyalomma plumbeum plumbeum ixodic tick which occurs in large numbers in the steppe districts of all the above-mentioned areas of the Crimean hemorrhagic fever (Crimea, Bulgaria, Krasnodar kray, Astrakhan oblast, the Central Asiatic Republic). The only way a person can be infected with the Crimean hemorrhagic fever under natural conditions is by the bite of an infected tick.

(This latest name of the above-mentioned tick, taken from B. I. Pomyerantsev's tick-name finder, is currently used in the literature on zoology in place of the old name of the tick Hyalomma marginatum marginatum Koch.)

Inasmuch as Hyalomma plumbeum plumbeum under natural conditions is found to be spontaneously infected with the virus of the Crimean hemorrhagic fever and capable of its ovarian transmission to its progeny and retention during the inter-epidemic period (in winter),

it may be considered as established that this tick is also the reservoir of the virus in nature. There are no definite data on the presence of a natural reservoir of the virus among vertebrates.

An investigation of wild rabbits for the virus-carrying capacity in the blood produced negative results (M. P. Chumakov, 1954). It is known, however, that among the rodents young rabbits and mice are partially susceptible to the virus of the crimean hemorrhagic fever, which points to the possibility of the rodents' participation in maintaining the infection in the ticks.

The Hyalomma plumbeum plumbeum ticks do not necessarily come into direct contact with man. Large quantities of this tick's larvae and nymphae parasitize rabbits which, according to A. G. Grobov, S. P. Pyontovskaya, and P. P. Porfilyev are most responsible for the dissemination and breeding of the ticks in the steppe areas of the Crimea. The ticks can spread from their natural biotopes to those created by men (cow barns, stables). In these cases the cattle can become the secondary host to the imaginal stage of the tick. People coming in contact with adult ticks and nymphae are attacked by them.

Inasmuch as the Hyalomma plumbeum plumbeum is both the carrier and reservoir of the virus in nature, the epidemiology of the disease is naturally determined in large measure by the ecology and biology of the tick.

The spread of the disease is limited to the areas inhabited by the carrier tick and observed only in the rural steppe areas among the population engaged in agricultural work.

Cases of the disease are scattered over a large territory and do not reveal any visible connection with one another. In the case of the Crimean hemorrhagic fever there is no information available on the possibility of aerial, aqueous, or toxic-elementary methods of infection. The disease, as a rule, is not transmitted by contact with an ill person. But cases of infection of the medical personnel in hospitals, blood donors, and patients in the neighboring wards suffering from the infection contacted from other patients with symptoms of the Crimean hemorrhagic fever occurred in the Crimean and fairly frequently also in certain Central Asiatic republics and in Bulgaria (1953). Such cases occurred when the infected blood of a patient came in contact with skin lesions of donors in the process of blood transfusion, as well as doctors and nurses working to stop the patient's hemmorrhage, due to the use of an unsterilized Frank needle. Infections in the hospital are still very rare occurrences; in the majority of cases contact with the blood of bleeding patients does not produce the disease. M. P. Chumakov (1954) believes that a mixed infection was probably involved in the occurrence of intra-hospital diseases: the virus of Crimean hemorrhagic fever and an unknown septic microorganism.

The active season of the Hyalomma plumbeum plumbeum ticks begins in April, reaches its maximum in July, and tapers off in August-September. In the steppes the ticks are found on the ground, in the grass, in the crops, on cattle, and they may attack people.

The disease is strictly seasonal, occurring in the spring-summer period with the highest incidence taking place in July-August. The incidence curve almost coincides with that of the attack on animals and people by ticks in their adult stage.

Patients recovering from the Crimean hemorrhagic fever acquire a reliable immunity which develops soon after the temperature has dropped to normal. Their nonsusceptibility to a recurrent infection is accompanied by the emergence of virus-neutralizing specific antibodies in the blood. A strong-enough immunity to massive infection is noted a year after the disease but that period is apparently not final (M. P. Chumakov).

Pathogenesis and pathological anatomy. Under natural conditions a person is infected by the bite of an infected tick. The clinical picture of the disease becomes clear in 3 to 7 days after the infection. In the first 3-5 days of the fever period the virus is regularly found in the patient's blood (M. P. Chumakov).

The pathogenesis of the disease has not been adequately studied. It may be assumed, however, that it is based on the same pathogenic processes occurring in the development of other hemorrhagic fevers (Omsk hemorrhagic fever, hemorrhagic nephrosonephritis).

Apparently the decisive factor in the pathogenesis is the affection of the vegetative nervous system including the disruption of the vascular innervation (A. A. Kolachev, T. A. Shutova) and the simultaneous immediate affect of the virus on the vascular wall. Moreover, the disruption of the functions of the hemopoietic apparatus, the reduction of the prothrombin level, and the retardation of the blood coagulability play an important part in the pathogenesis of the disease (V. M. Domrachev, T. A. Shutova, V. V. Kartasheva, G. N. Pershin, N. S. Slavina, quoted from M. P. Chumakov, 1947, 1954).

The disruption of the vascular innervation, as well as the virus action on the vascular wall, result in the destruction of the cappillaries and the development of symptoms of hemorrhagic diathesis, which are prominent features of the clinical picture of the disease. The disruption of blood coagulability observed in severe cases aggravates the hemorrhagic syndrome.

It may be assumed that the vascular disorder is responsible for the development of hypoxemia and the profound disruption of the tissular exchange, which intensifies the intoxication still further and causes the degeneration of the nerve cells and parenchymatous organs.

The basic pathoanatomical changes consist in numerous hemorrhages in the internal organ tissues, bleeding in the gastric and intestinal cavity, as well as the affection of the skin vessels in the form of a hemorrhagic rash or cutaneous purpura. A microscopic investigation reveals hemorrhages of various magnitude in almost all the organs. At the same time, degenerative cell changes develop in the liver and the nodes of the vegetative nervous system and inflammatory symptoms are observed in the lungs.

The clinical picture. The incubation period of the Crimean hemorrhagic fever fluctuates from 2 to 7 days.

The onset of the disease is acute and prodromal symptoms, as a rule, are absent. The first days the temperature goes up to 39-40° and remains at a high level for 5 to 15 days. The fever chart is nonuniform and remittent and the falling temperature produces a step-like curve. In about 80% of the cases the fever occurs in 2 phases forming a 2-hump curve with a 1-day's drop to a subfebrile level between the 3rd and 5th day of the disease.

The initial period of the disease covers the first 3-5 days before the appearance of a rash and other symptoms of hemorrhagic diathesis and is characterized by the symptoms common to all cases of hemorrhagic fever: a high temperature and general toxic syndrome.

As in most of the febrile disease, the patients usually complain of severe headaches and pains in the muscles and the whole body, weakness, sluggishness, and occasional vomiting.

An objective investigation made in the initial period also reveals symptoms common to the majority of hemorrhagic fever cases. A pronounced hyperemia of the face and neck, as well as a hyperemia of the pharynx with an injection of the lingual vessels, and observed. The skin is very dry to the touch. The internal organs reveal no pronounced changes during that period.

The critical period of the disease begins with symptoms of hemorrhagic diathesis which develop between the 3rd and 6th day of the disease in 75-90% of the patients and are the most characteristic indications of the Crimean hemorrhagic fever. The temperature usually begins to fall with the appearance of the hemorrhagic syndrome. In case of a short fever period (4-5 days), hemorrhagic symptoms may develop in the course of the falling temperature or after it has dropped to normal.

One of the most characteristic symptoms of hemorrhage diathesis is an enanthema on the mucous membrane and exanthema on the body of the patients.

Rashes may vary in intensity and nature from small and meager petechiae the size of a pinhead to large ecchymoses measuring 5-8 cm; in milder cases the rash may be of a roseolar type. Ordinarily the rash is not heavy, it occurs in the axillary fossae, on the lateral sides of the thorax, and on the internal surfaces of the shoulders and, less frequently, in the subclavicular and supraclavicular areas. The exanthema persists for several days and then begins to pale, taking on a brownish color; in some patients the disappearance of the exanthema is followed by a skin desquamation.

An enanthema in the patient's pharynx, which is very important for an early diagnosis, can be found simultaneously with the outbreak of the rash and sometimes 1-2 days before its outbreak.

Konchalovskiy's symptom (applying a tourniquet) and the pinch symptom in the period are, as a rule, positive.

A number of other hemorrhagic symptoms develop during the critical stage of the disease in addition to a rash. Nosebleeds and a bleeding mucous membrane of the oral cavity are noted in typical cases. Bloody vomit and intestinal bleeding are observed in several cases; this is occasionally accompanied by hemorrhages in the lungs, kidney parenchyma, and pelvis, as well as metrorrhagia and oral bleeding. Pronounced hemorrhages may be absent in mild and very mild cases of the disease, in which case microhematuria and the presence of fresh erythrocytes are found in the patient's excrements.

It should be pointed that the hemorrhagic syndrome to the Crimean hemorrhagic fever is considerably more pronounced than that of the Omsk hemorrhagic fever or the hemorrhagic nephrosonephritis.

In the critical period of the disease the condition of the patients deteriorates. Symptoms of intoxication remain or even increase. The severity of the headaches and muscular pain increases, as does the general weakness, and there is a complete loss of appetite; the patient feels a sensation of dryness in the mouth and he is tortured by thirst. The patients are sluggish, adynamic, and frequently delirious at night.

A relative bradycardia is usually observed in the cardiovascular system; the pulse is soft, rhythmic, occasionally revealing an extrasystole in severe cases. The heart is not enlarged. The heart tones are somewhat dulled and transitional murmurs are occasionally heard.

In severe and average cases the arterial pressure drops fairly rapidly. The pulse pressure dropps to 30-40 mm on the mercury column. The developing hypotonia persists for a long time even during the recovery period.

Unlike the case in Omsk hemorrhagic fever, the respiratory organs are comparatively seldom affected by the Crimean hemorrhagic fever.

In severe cases the inflammatory processes brought about by the pulmonary hemorrhages may be accompanied by the development of recurrent focal pheumonia which is not connected with the hemorrhages. Pneumonia aggravates the disease to a considerable extent and prolongs the recovery period.

The changes in the digestive organs are frequently manifested by vomiting and, occasionally, by diarrhea. As pointed out above, blood vomiting may develop in severe cases. Some patients develop profuse intestinal bleeding which is of a diffuse capillary nature and poses a serious threat to the life of the patient; it could result in a fatal outcome on the 7th-8th day of the disease.

The loss of appetite is as a rule observed, the tongue is covered with a reddish coating, there is bleeding from the mucous membrane of the oral cavity and a bad odor from the mouth. In many patients the Gregerson reaction is found to be positive.

The liver and spleen are enlarged in only 20-25% of the cases (A. A. Kolachev), and M. P. Chumakov points out that they are painful to the touch and calls attention to the bilirubanemia developing during the fever period. These data show that the liver is involved in the disease process.

Kidney changes are observed in the great majority of the patients (V. V. Kartasheva). But they are, as a rule, moderate and usually in the nature of an infection-toxic nepropathy. The pathology of the kidneys is manifested in albuminuria (up to 3‰) and cylindruria. A pronounced hematuria is not often observed; no edemas are noted. The reaction to urobilin is, as a rule, positive. Pasternak's symptom is negative.

The nervous system undergoes definite changes. According to the data obtained by T. A. Shutova and N. P. Sorokina, 100% of the patients suffer from headaches, 12% are delirious, and 44% of the investigated patients reveal temporary mile disorders of the cerebrocranial nerves. Hypokinesis and an increase in tendon reflexes are also observed in a considerable number of patients. Finally, 6% of the patients reveal a positive Babinskiy symptom, 12% a Gordon symptom, and 10% an Oppenheim symptom.

The disruption of the vegetative nervous system basically amounts to an inhibition of the sympathetic nervous system.

The peripheral blood picture during the critical stage is quite characteristic. The temporary blood coagulation in the initial period (V. V. Kartashyeva) is followed by the development of a hypochromic anemia which may rise to a very high degree in view of the profuse bleeding. The number of erythrocytes may be reduced to 1,580,000 per 1 cm^3 and the hemoglobin may drop to 20% (V. M. Domrachev).

Leucopenia (up to 3,500-1,400 per 1 mm^3), neutropenia with a sharp stapnuclear shift, relative lymphocytosis, aneoxenophilia, and occasionally also monocytosis are frequently observed in the leucocytes.

Leucopenia is frequently accompanied by the development of thrombopenia (up to 60,000-18,000 thrombocytes per 1 mm^3) and, what is particularly important, by a sharp reduction in the number of prothrombins and a temporary reduction in blood coagulability when the bleeding is of normal duration. This is indicative of an acute though unstable disruption and the development of hemorrhagic syndrome (M. P. Chumakov).

The erythrocyte sedimentation reaction at the beginning of the disease is somewhat retarded; it is accelerated to a high level during the critical stage (V. M. Domrachev).

Following are the principal characteristic clinical symptoms peculiar to the critical stage of the Crimean hemorrhagic fever:

1) pronounced generalized toxic manifestations and a high temperature which in wome cases goes down by the end of the first week;
2) symptoms of hemorrhagic diathesis;
3) frequent changes on the part of the nervous system;
4) a characteristic picture of the blood and a disruption of the blood clotting mechanism.

In addition to distinctly hemorrhagic types of the disease, the Crimean hemorrhagic fever may take a mild and asymptomatic course. In such cases the disease is accompanied by a 3 to 10-day fever period, headaches, conjunctivitas, and occasionally an enanthema and temporary roseolar rash. An investigation of the blood reveals the usual picture:

leucopenia, neutropenia, and thrombopenia. The hemorrhagic diathesis symptoms are not pronounced. That such cases are related to the Crimean hemorrhagic fever was proved (M. P. Chumakov) by serological and virusological investigation.

The complications are, as a rule, of a septic nature. They develop during the critical stage and are manifested in secondary necrotic anginae, parotitis phlegmonosa, pyelonephritis, and occasionally in the development of peritonitis. In severe cases the disease is complicated bypneumonia, which aggravates the course of the disease.

Prognosis. In the majority of cases the prognosis is favorable. The mortality amounts to only 3%. The capacity for work is restored within a few weeks.

Diagnosis. When diagnosing the Crimean hemorrhagic fever we must, first of all, rule out such infectious diseases as the grippe, typhus, dengue, yellow fever, Pappataci fever, as well as a number of diseases of a noninfectious etiology such as scurvy, the Schonlein-Henoch disease, and alimentary-toxic aleukia.

The Crimean hemorrhagic fever should then be singled out from the other known types of hemorrhagic fever.

The Crimean hemorrhagic fever is more severe than the Omsk type, and is accompanied by a more pronounced hemorrhagic syndrome and a higher mortality (the mortality of the Omsk hemorrhagic fever does not exceed 1%). Moreover, the affection of the respiratory apparatus, so typical of the Omsk hemorrhagic fever, is not usually observed in the case of the Crimean hemorrhagic fever.

The difference between the Crimean hemorrhagic fever and hemorrhagic nephrosonephritis is that the former does not occur during the winter, has a more pronounced hemorrhagic syndrome, leucopenia in the blood and, what is most important, has no characteristic renal syndrome.

Laboratory diagnosis. The virus is found in the patient's blood during the first 3-5 days of the fever period; specific antibodies may appear in the blood beginning with the second week.

A bacteriological diagnosis can be made with the aid of a complement-fixation reaction (L. M. Khai, M. P. Chumakov and A. P. Belyayeva) and a neutral reaction. Of practical importance for the clinical picture is the complement-fixation reaction used for finding antibodies in the blood of the patients and convalescents; the reaction produces positive results at the end of the first week of the disease. Available data indicate that the complement-fixation reaction, carried out by the V. I. Ioffe method (in cold temperature), makes it possible to find viral antigens in the patient's blood as early as 10-12 hours after the onset of the disease and produces positive results for 3-5 days. Under such conditions the reaction may be used for an early laboratory diagnosis.

The neutral reaction is used only for a retrospective diagnosis and is carried out with the serum of a convalescing or former patient.

Treatment. The serum of convalescing patients can be used as an effective specific method of treatment (M. P. Chumakov). The blood is taken from recovered patients between the 30th and 40th day of the disease. The serum is introduced intramuscularly in doses of 20-40 ml on 3 consecutive days. In view of the limited quantity of the serum, however, serotherapy is used only in the treatment of severe cases threatened with the development of hemorrhagic diathesis.

The treatment usually amounts to symptomatic therapy and is designed to reduce the toxicosis and hemorrhagic occurrences.

The patients should be hospitalized as soon as possible, confined to bed, and provided with good care. Intravenous injection of ascorbic acid, a 10% solution of sodium chloride, and vitamin K are used for fighting hemorrhagic diathesis.

The patients require a large intake of liquid, and intravenous injections of a 40% glucose solution combined with a subcutaneous introduction of insulin, in order to reduce intoxication.

Recommended as cardiac drugs are caffeine, cordiamine, diuratin, ephedrine, and camphor in the usual doses.

In case of severe headaches the use of pyramidon and phenacetin is advisable. Pantopon should be prescribed for severe pains and sleepliness.

Penicillin is used for the treatment of septic complications. Sulfa drugs or penicillin should be used when recurrent pneumonia develops.

The patient should be confined to bed 1-2 weeks after the temperature has dropped to normal.

Prophylaxis. The prophylactic measures against the Crimean hemorrhagic fever consist in fighting the carrier ticks (see Omsk hemorrhagic fever, prophylaxis section, p. 112 of text [orig.]). Of some prophylactic importance also are the measures designed to destroy the rabbits and other steppe rodents which the ticks parasitize.

No specific prophylactic measures against the Crimean hemorrhagic fever have been developed.

Hemorrhagic Nephorosonephritis

Syonyms: infectious nephrosonephritis; endemic nephrosonephritis (Soviet literature), Far Eastern hemorrhagic fever (American literature), epidemic hemorrhagic fever (Japanese literature), epidemic hemorrhagic purpura (Japanese literature), hemorrhagic fever with a renal syndrome (A. I. Reznikov, M. P. Chumakov).

Definition. Hemorrhagic nephrosonephritis is an acute febrile disease of a viral etiology occurring in the Soviet Union (Far East, Yaroslav and Kalinin oblasts, the Urals, Transcarpathian Ukraine, and certain other oblasts), China (Manchuria, and Korea. The disease is characterized by fever, toxicosis, and occurrences of hemorrhagic diathesis and is regularly accompanied by a more or less severe affection of the kidneys. Rodents of the Muridae family and certain ticks of the Gamasidae family are the reservoir of the virus; the method of transmitting the infection to man has not been definitely established.

History. Cases of the disease whose clinical picture resembles hemorrhagic nephrosonephritis were observed in the Far East early in the twentieth century and described as "Manchurian gastritis." It is natural to assume in this connection that many other cases of that disease were recorded under different and erroneous diagnoses.

A systematic study of hemorrhagic nephrosonephritis was begun in 1935-1937 when the disease became more widespread in the Far East and revealed a high degree of mortality.

It was learned in the postwar years that an outbreak of a similar disease (over 500 cases) occurred in 1936-1943 in the Japanese army stationed in Manchuria, particularly in the areas bordering on the USSR; in 1941 the Japanese called that epidemic hemorrhagic fever.

About 2,100 cases of the disease, called Far Eastern hemorrhagic fever, broke out in 1951-1953 during the Korean War in the areas south of the 38th parallel (primarily among the American troops). There are indications that the disease has existed in China since times immemorial.

An identical or very similar disease was first discovered in 1948-1954 in the European part of the USSR and studied in detail in the Yaroslav and Kalinin oblasts (M. P. Chumakov, A. E. Reznikov, A. A. Avakyan, A. D. Lebedev and S. G. Dzarurov, S. G. Drozdov, S. L. Glazunov, E. V. Leshchinskaya, etc.), in the Transcarpathian oblast (A. A. Avakyan and S. V. Shimshelevitch, 1953), in the Ural region (N. N. Solomin, B. L. Ugrumov and V. P. Gorbatsevitch, 1953), and the south Ukraine.

In the Soviet Union hemorrhagic nephrosonephritis was singled out as an independent disease in 1935 in the Far East by A. V. Churilov, A. M. Cherevkov, G. M. Tsygankov, and A. I. Reznikov. In Japan the disease is described in the works of Kitano, Kasaxhara, Takami, Ikeda, and others (1940-1953).

To study the new disease, the USSR Ministry of Health sent 4 expeditions to the Far East between 1938 and 1947 headed by V. I. Tarasov (1938), V. I. Terskikh (1938), I. I. Rogozin and A. A. Smorodintsev (1939-1940), A. A. Smorodintsev (1946-1947). Similar complex expeditions headed by M. P. Chumakov and A. A. Avakyan were working between 1949 and 1955 in the disease-affected areas of the upper Volga basin and Transcarpathia.

The result of many years of systematic work on the part of a large body of Soviet physicians was the establishment of the viral

etiology and epidemiological characteristics of the disease (A. A. Smorodintsev, V. I. Terskikh, I. I. Rogozin, K. A. Kokhreidze, V. D. Neustroyev, M. R. Smirnov, A. K. Shubladze, U. S. Sergeyeva, M. P. Chumakov, A. P. Belayeva, A. A. Avakyan, A. D. Lebedev, etc.). The pathological anatomy and certain features of the pathogenesis of hemorrhagic nephrosonephritis are reflected in the works of L. A. Leybin, V. G. Chudakov, G. P. Milash, and A. G. Kestner. The description of the clinical picture and the methods of diagnosing the disease is credited to A. V. Churilov, G. M. Tsygankov, A. I. Rosenkov, E. A. Galperin, S. S. Rotenburg, S. H. I. Ratner, L. I. Kazbintsev and M. I. Dunayevskiy, etc. Finally, the materials on hemorrhagic nephrosonephritis have in recent years been generalized in monegraphs by N. I. Ragoz and G. M. Tsygankov (1952) and A. A. Smorodintsev, V. G. Chudakov, and A. V. Churilov (1953).

Etiology. The first proofs of the viral etiology of hemorrhagic nephrosonephritis were obtained in 1940 in the Far East by A. A. Smorodintsev, V. D. Neustroyev, U. S. Sergeyev, and A. V. Churilov in their observations of volunteers. It has now been learned that in 1940-1941 Japanese investigators (Kitano and others) also obtained experimental data in favor of the viral etiology of the Far Eastern hemorrhagic fever. The viral nature of hemorrhagic fever with the renal syndrome was again established in 1950-1955 in Yaroslav and Kalinin oblasts by M. P. Chumakov and A. P. Belayeva.

The causative agent of hemorrhagic nephrosonephritis, a filtrable virus called Haemorrhagogenes nephritidis, is found in the patient's blood and urine (A. A. Smorodintsev and M. P. Chumakov) in the first 5 days of the fever period, as well as in certain types of the Gamasidae family ticks which parasitize field mice, vield voles, and other rodents (M. P. Chumakov, etc., 1955). According to A. A. Smorodintsev (1954), the virus is found in the blood of infected eastern field voles kept in close contact with one another for a week.

According to M. P. Chumakov (1954), as well as the Japanese and American investigators, it is impossible to sustain the virus in the laboratory, as it does not infect laboratory animals or chicken embryos. But A. A. Smorodintsev reported (1953) a successful infection of chicken embryos and also a partial susceptibility of eastern field voles. Following an intraperitoneal introduction of infected blood or urine, the eastern field-voles developed a non-fatal disease with an enlarged spleen with occasional hemorrhages in it. Further tests on the eastern field voles resulted in the gradual weakening of the spleen's reaction to the infection.

A. A. Smorodintsev succeeded in reproducing the disease in cats by an intraperitoneal or intracardiac infection; but consecutive injections developed a secondary infection in the cats, complicating the study of hemorrhagic nephrosonephritis in this type of animal.

Almost all of the methods used so far to reproduce the infection in the laboratory failed to produce any clear-cut positive or regular results in view of the absence of a fairly reliable experimental model (M. P. Chumakov, 1954).

Serological investigations revealed the absence of a cross reaction to other hemorrhagic fevers and confirm the etiological independence of hemorrhagic nephrosonephritis.

Epidemiology. Before 1948 hemorrhagic nephrosonephritis was believed to be a disease specific only to the Far East (the Maritime and Khabarovsk krays) and Manchuria. Similar diseases were discovered in a number of oblasts in the European part of the USSR in 1948-1954 and in Korea in 1951-1953.

In the Far East the disease occurs in the rural forest-steppe areas with a warm climate covering the lowlands and inhabited by large numbers of rodents of the Muridae family. In the Yaroslav and Kalinin oblasts the affected areas represent a single endemic zone on the left bank of the Volga (mostly lowland wooded and open places). So far only the Gamasidae-type Laeleps pavlovskii ticks, certain nidus Gamasidae-type ticks -- Eugamasus nidi and Haemolaeleps glasgowi -- and certain types of lyponyssus ticks have proved to be the reservoir of hemorrhagic nephrosonephritis (M. P. Chumakov and others, 1955). The presence of an infection reservoir among the Muridae rodents, the hosts to the mentioned ticks, is quite probable but requires additional experimental proof. According to A. A. Smorodintsev, the reservoir of the hemorrhagic nephrosonephritis in the Far East is the Mikhnov eastern field vole.

Japanese and American researchers believe that the Apodemus agrarius field mouse is the probable reservoir of infection of man in Manchuria and Korea. The Mikhnov eastern field vole is not found in the source-areas of hemorrhagic nephrosonephritis in the upper Volga basin but field mice (Apodemus agrarius), ordinary field voles, and other Muridae rodents are found in abundance.

The method of infecting people under natural conditions has not yet been finally ascertained. It is possible that the infection occurs during the contact between man and the infected secretion of Muridae rodents suffering from a latent disease. Many investigators assume the possibility of the infection being transmitted by the bites of ectoparasites on rodents (Gamasidae-type ticks, fleas), when attacking a person (A. A. Smorodintsev, 1953). In the upper Volga basin, where the diseases occurred primarily in wintertime (November-December), there has been no evidence of attacks on people by ticks and fleas. It is believed that the Gamasidae-type ticks are the carriers of the infection between the rodents (M. P. Chumakov, 1954, 1955).

In the Far East the mostly likely subjects of infection are the people living in the wilderness. In the infection areas located in the European part of the USSR, people have been infected in their own houses or at work in the outbuildings where large concentrations of Muridae-type rodents are found in the autumn.

A. A. Smorodintsev's observations show that it is impossible to infect people through the mucous membranes of the upper respiratory tracts or gastro-intestinal tract but that the virus can easily multiply in an organism infected through injured skin. But it is still impossible to rule out with any degree of certainty the possibility of people becoming infected through the oral mucosae or upper respiratory tract (M. P. Chumakov).

Hemorrhagic nephrosonephritis is sporadic in about 90% of the cases, but the group diseases accounting for about 10% of all the cases may represent explosive outbreaks increasing in scope within the first 4-5 days but rapidly disappearing in the following 15-20 days. The average duration of an outbreak in the Far East amounted to 20-25 days (A. A. Smorodintsev, A. M. Chudakov, A. V. Churilov); in the infection areas of the upper Volga basin the duration of the autumn-winter incidence of the disease was 2-2½ months. Characteristic of the disease were the complete absence of contagiousity among people.

The incidence of hemorrhagic nephrosonephritis in the Far East occurs in the summer-autumn season, rising in June-July and September-October; the number of cases is reduced in wintertime and increases again in May-June. In the upper Volga basin up to 90% of all the cases were observed in the fall and winter (November-December, January, and occasionally February). The rising incidence-curve in the autumn-winter months can be explained by the seasonal migration of the field rodents to human dwellings. The year-round existence of the disease is due to the constant presence of some type of field rodent in the peoples' homes.

The spring-summer increase in the incidence in the Far East is apparently due to the people's increased contact with nature in the raw

A persistent infection of an endemic nature (recurrence of the disease for many years) in certain houses of a settlement, and in adjoining and other houses of the same settlement has been observed in the infection areas of the upper Volga basin. M. P. Chumakov (1955) believes that this is due to the reservoir of infection represented by the nidal Gamasidae-type ticks which do not leave the house but transmit the virus in the seasonal period "as in a relay race" to the field rodents gathering in the homes and outbuildings by that time. That opinion is confirmed by the presence of the virus in the nidal Gamasidae-type ticks.

All persons in contact with nature in the endemic areas, regardless of sex or age, are subject to the disease in the Far East (N. I. Ragoza and G. M. Tsygankov). Comparatively few children have been affected by the disease in the infection areas of the European part of the USSR; this is possibly due to their insignificant contact with field rodents in the outbuildings and under natural conditions. The disease is followed by the development of a stable immunity; the recurrence of the disease has not been observed.

Pathological anatomy. The pathoanatomical changes observable in hemorrhagic nephrosonephritis are characterized by manifestations of of hemorrhagic diathesis, the affection of the kidneys, and changes in other organs and tissues.

A pathohisological investigation reveals hemorrhages in various organs. Punctate and larger discharges appear in the skin, sclera, mucous membranes, subcutaneous tissue, mesentery, intestines and parenchymatous organs. Diffuse destructive inflammatory changes of a focal nature frequently resulting in the rupture of the vascular wall are observed in the vessels, particularly the capillaries and precapillarries. These changes are particularly pronounced in the intertubular vessels of the substantia medullaris of the kidneys.

The cerebrum is plethoric, revealing the presence of stases, focal affections of the small vessels, and discharges. Pronounced degenerative-necrotic changes are observed in the nerve cells. The infection of the occipital sympathetic nodes and the solar gaglion nodes is manifested as a sharp plethora, and discharges and degenerative changes in the ganglionic cells.

The pathoanatomical changes of the kidneys are quite typical: the kidneys are enlarged and flaccid and the capsule is easily removable; punctate or larger discharges are visible under the capsule. A cross-section reveals a swelling of the corticle substance; its thickness is uneven and its color is rose- or grayish-yellow with scattered red dots. The pyramids are dark red and their outlines are indistinct. In some places the pyramids take on a gray color, which is an indication of a developing necrosis. The mucosa of the urinary tracts and particularly the pelvis is hyperemic and covered with discharges.

The pathological process in the kidneys, according to V. G. Chudakov, is sharply pronounced and involves all the elements of the nephrons, stroma, and vessels; it is of a focal glomerulonephritic nature. The epithelia of the winding and straight canaliculi are subjected to a turbid swelling and granular decomposition; the desquamation of the necrotized epitheleum is noted in some areas. Extensive discharges are found in the stroma of the pyramids. Some of the glomeruli do not undergo any morphological changes. A proliferation of the epithelium of Bowman's capsule is observed in some places, isolated glomeruli are found to be homogenized, and infiltrates of lymphoid cells and histiocytes are occasionally found in the glomeruli around the vessels.

L. S. Leyben believes, however, that the glomeruli are not greatly involved and that the major changes affect primarily the canalicular apparatus of the kidneys, causing their destruction and necrosis as a result of the severe disruption of the blood circulation.

At the same time, diffuse dystrophic changes occur in many ductless glands (adrenal, hypophysis, and thyroid gland), in the liver and heart muscle. The accompanying vascular disorders result in the development of necroses in various organs. A secondary infection coming on top of these profound changes frequently complicates the course of the disease.

The clinical picture. The incubation period of hemorrhagic neprhosonephritis fluctuates from 11 to 23 days, averaging 15 days.

The prodromal period, studied in cases of experimental infection, lasts 2-4 days and is characterized by a normal or subfebrile temperature, sluggishness, apathy, poor appetite and an occasional development of catarrhal angina. The patients are usually not confined to bed during this period, and the onset of the disease is overlooked.

The disease begins with a sharp rise in temperature which goes up to 30-40° on the first day, remaining at that level 2-6 days and longer. The temperature then drops to normal in 2-3 days (a shortened lysis). A critical reduction of the temperature is noted in some cases; the temperature drop is sometimes of a lytic nature. Thus the fever period lasts from 4 to 9 days. A second fever-wave, usually milder than the first, may be observed in some of the patients (in 48% of the cases according to N. I. Ragoza and G. M. Tsygankov) for 10-15 days after the temperature has dropped to normal.

The initial phase of the disease covers the period between the temperature rise and the appearance of symptoms of hemorrhagic diathesis and lasts about 2-4 days. The development of the disease is very violent. The rising temperature on the first day is accompanied by a sensation of warmth, severe headaches, a jaded feeling, and pains all over the body, especially in the loins, abdomen, and the muscles of the lower extremities. The appetite, as a rule, is absent, and nausea and vomiting are noted. Other developments include constipation, a sensation of dryness in the mouth, thirst, and oliguria.

The patient's mind is confused from the very first days of the disease. Sluggishness and apathy are observed. The patient's is hyperemic: the hyperemia occasionally spreads to the neck, chest, and upper extremities; the conjunctiva of the eyelids and sclera and inflamed.

The pulse frequency in most cases lags behind the temperature. No definite changes are found during this period in the internal organs. A very important early diagnostic symptom is the Pasternatskiy bilateral symptom observable in the initial period.

Characteristic changes are found in the central nervous system. In cases with a clear clinical picture, the severe headaches, vomiting, sluggishness, and inhibition of the patient are accompanied by manifestations of meningism or even a mild meningitis. Observed in these patients is a rigidity of the occipital muscles and Kernig and Brudzinskiy positive symptoms; Gordon's and Oppenheim's symptoms occasionally appear, as does a weakening or unevenness of abdominal reflexes. A spinal puncture reveals a higher fluid pressure and an increased content of albumin (up to 0.132%). Observable also during this period of the disease are symptoms of oral automatism (nasolabial, sucking, sensing, and mental reflexes) which indicate that the cerebral cortex is involved in the pathological process.

The initial period is thus characterized by:

1) an acute onset with a high temperature;

2) pronounced general toxic occurrences with indications that the central nervous system is affected;

3) symptoms of an early affection of the kidneys (pain in the waistline, a positive Pasternitskiy symptom, etc.);

4) hyperemia of the facial skin, neck, pharynx, mucosa, and the conjunctiva vessels of the eyelids and sclera.

The critical period of the disease begins with symptoms of hemorrhagic diathesis (between the 3rd and 5th day of the disease) and continues until a reverse development of the pathological changes begins in the kidneys (the appearance of polyuria).

The critical period of hemorrhagic nephrosonephritis consists of 2 stages: the first, fever stage, is characterized by hemorrhagic manifestations arising against a background of high temperature and general toxic occurrences; the second, a febrile stage, is characterized by a normal temperature and an aggravated disfunction of the kidneys.

1. The febrile stage of the critical period begins between the 3rd and 5th day of the disease with symptoms of hemorrhagic diathesis and ends with a temperature dropping to normal. A petechial rash, one of the typical symptoms, is observed in 95% of the cases (A. V. Churilov) and localized mostly on the lateral surfaces of the body in the area of the brachial belt and on the internal brachium surfaces. The rash outbreak continues from the 3rd to 5th day of the disease to the end of the fever period; in some cases the rash covers the entire body. There is a further likelihood of discharges into the conjunctiva of the eyelids or sclera (which is a very typical symptom), hemorrhages at the points of subcutaneous injection, nose and gum bleeding, blood vomit and blood stool.

An enanthema is revealed between the 3rd and 4th day of the disease in the form of punctate discharges on the mucous membranes of the palate and lower lip; it has a great diagnostic value, as its appearance is preceeded by a petechial rash on the skin (A. V. Churilov, S. S. Rotenburg).

The pinch symptom and Konchalovskiy's symptom, indicating changes in the small vessels, are, as a rule, positive during the critical stage.

The patient's condition deteriorates in the beginning of the critical stage of the disease and becomes serious in clinically pronounced cases. The patient's mind is depressed; he is sluggish, apathetic, annoyed by severe headaches, sharp pains in the waistline and abdomen, thirst, as well as painful nausea and vomiting. Occasionally he lapses into delirium, restlessness, and hallucinations; a complete loss of consciousness is observable in very ill patients. The patient's face becomes hyperemic, his tongue dry and coated.

In most patients the cardiovascular system may be characterized by a relative bradycardia, a moderate reduction of the maximum arterial pressure, as well as muted heart tones. The heart is seldom enlarged (N. I. Ragoza, G. M. Tsygankov).

No substantial changes are noted in the respiratory organs. Bronchitic symptoms are found in the lungs.

The digestive organs are subjected to considerable changes. The tongue is dry and covered with a thin grayish or greenish coating (A. V. Churilov), the pharynx is highly hyperemic, and occasional bleeding is observed in the gums. An unpleasant odor of putrid blood comes from the mouth. The vomiting observed from the very first day of the disease continues throughout the fever period, occasionally becoming uncontrollable. In some cases blood stains are found in the vomitus. The complete lack of appetite is accompanied by the development of an intense thirst. In addition to vomiting, the patients are also very much annoyed by hiccuping which, according to A. V. Churilov, is observed in one third of the cases. Abdominal pains of no definite localization are a substantial and occasionally major feature of the febrile stage of the critical period. The stool is, as a rule, retained. Evacuation occasionally increases to 5 times a day and becomes sanguinolent.

In the majority of cases the liver and spleen are not enlarged.

Distinct pathological changes are observed in the kidneys. The oliguria sometimes develops into a full anuria. The specific gravity of the urine drops to 1.010-1.002. Albuminuria develops on the 5th or 6th day of the disease. The number of erythrocytes found in the urine is so large that it often takes on the color of meat swill /sic/. Special vacuolized cells and occasionally the first "fibrinous" cylinders appear in the urine at the end of the fever period.

In some of the cases meningeal symptoms are found in the nervous system.

Thus the febrile stage of the critical period is characterized by:

1) a high temperature;
2) symptoms of hemorrhagic diathesis;
3) a pronounced toxicosis and the affection of the central nervous system;
4) manifestations on the part of the digestive organs;
5) changes in the kidneys which in this particular period do not play a leading part in the clinical picture.

Between the 4th and 9th days after the onset of the disease, the temperature drops to normal and the second, afebrile, stage of the critical period sets in.

2. The afebrile stage of the critical period continues until the recovery period, which is first symptomized by polyuria. The major indication of this stage of the disease is a growing disfunction of the kidneys.

Despite the falling temperature, the patient's condition does not improve; occasionally it even becomes more aggravated. The patients remain sluggish and are troubled by nausea, vomiting, and hiccuping; the appetite is absent and the headaches do not stop; the pain in the abdomen and waistline continues.

The patient's appearance undergoes a change. The hyperemia disappears from the face, but the conjunctiva of the eyelids and sclera remain bloodshot. The skin on the body remains pale and dry and the face takes on a "lusterless" hue (N. I. Ragoza, G. M. Tsygankov). The symptoms of hemorrhagic diathesis, so typical of the febrile stage of the critical period, are subjected to a reverse development but are still noticeable (rash, discharges, bleeding, etc.). Profuse nasal, uterine, and intestinal bleeding may develop also after the temperature has dropped (A. V. Churilov).

As has been pointed out above, the major symptoms of this period are determined by the severe affection of the kidneys. The severe pain in the waistline and positive Pasternatskiy's symptom remain. The patients urinate very little and a complete anuria is sometimes observed. The quantity of albumin in the urine fluctuates from traces to 24°/oo. The most pronounced albuminuria noted in the last days of the febrile period remains also in the first days following the temperature drop and then rapidly disappears. Between the 9th and 13th day of the disease most of the patients reveal only traces of albumin (M. I. Dunayevskiy).

Small quantities of leucocytes, hyaline cylinders, and erythrocytes (microhematuria and occasionally macrohematuria) are found in the residue of the urine.

A characteristic feature of the urine residue are the unique large epithelial "vacuolized cells" occurring in the form of concentrations as well as the special "fibrinous" cylinders resembling ceraceous cylingers but exceeding them in size and covering several visual fields of the microscope (M. I. Dunayevskiy). These cylinders appear when the albuminuris is at its highest level and occur most frequently between the 10th and 12th day of the disease.

The severe disruptions of the kidney functions are responsible for the development of more or less pronounced uremic symptoms which are associated with increasing azotemia. The patients reveal a typical bad breath, nausea, vomiting, drowsiness, a dull mind, occasional skin itching, and a higher arterial pressure. Such a severe condition usually continues for a week; in favorable cases the symptoms of uremia disappear in proportion to the increasing diuresis.

The amount of residual nitrogen in the blood increases from the first day of the febrile period and reaches a maximum (60-200 mg%) in the first day of the falling temperature. The residual nitrogen decreases with the increasing quantity of urine and reaches the norm between the 15th and 22nd day of the disease (G. M. Tsygankov).

Cases of renal eclampsia are occasionally observed.

A distinct bradycardia and a reduction of arterial pressure (mostly a maximum) are observed in most cases of the disease in the cardiovascular system. A temporary increase in the arterial pressure is observed only in cases of uremia. The heart is occasionally enlarged (mostly toward the left), and its tones are muffled. An electrocardiogram reveals profound changes of the myocardium which are expressed by a reduction of all waves (N. I. Ragoza, G. M. Tsygankov).

No substantial changes are observed in that period in the respiratory system.

The digestive organs reveal the following symptoms: lack of appetite, a dry tongue, and a growing thirst, but the frequent nausea and vomiting prevent its quenching. Hiccuping continues to exhaust the patients. The abdominal pains do not stop and the stool is mostly retained, but occasional diarrhea is observed (N. I. Ragoza, G. M. Tsygankov).

Thus the second, afebrile, stage of the critical period is characterized by:

1) normal or low temperature;

2) a profound disruption of the kidney function with a more or less pronounced symptoms of uremia;

3) a pronounced intoxication and an aggravated condition of the patient;

4) symptoms revealed by the digestive organs (abdominal pain, vomiting, nausea, hiccuping).

Between the 4th and 6th day of this stage the condition of the patients begins to improve. The pains subside, nausea and hiccuping cease, the diuresis increases, and the pathological admixtures in the urine disappear. Finally, the daily quantity of urine exceeds the norm (1.5 liters); that day marks the beginning of the recovery period (N. I. Ragoza, G. M. Tsygankov).

In hemorrhagic nephrosonephritis, just as in the other hemorrhagic fevers, the recovery period is characterized by a lengthy and very slow restoration of the capacity for work. A pronounced polyuria remains up to 20 days and then gradually diminishes. The functional kidney tests made in that period indicate a lengthy disruption of the kidney function (a secretion test, and concentration test by the Zimnitskiy method); the restoration period of the kidney functions is protracted to 1-3 months.

The patients also feel weak, perspire, and reveal symptoms of cardiovascular insufficiency for a long time. After recovery, the kidney functions are completely restored; no development into chronic forms of the disease has been observed.

The blood picture (according to M. I. Dunayevskiy). The changes in the erythrocytes are insignificant and consist of a moderate hypochromic anemia which is most pronounced during the critical stage period.

Distinct and quite characteristic changes are observed in the leucocytes. Typical of the initial period of the disease is a leucopenia with a sharp stabnuclear shift of neutrophils and a reduced number or complete absence of eosinophils. The blood picture changes beginning with the 5th day of the disease. There develops an intense leucocytosis and a neutrophilia with a characteristic "motley" shift (stab-nuclear, immature, myelocytes and occasionally promyelocytes and myeloblasts), and a large quantity of plasmatic cells appears; the number of lymphocytes is reduced to 10-20%.

At the end of the febrile period the number of leucocytes becomes normal or slightly increased, the mentioned changes of the leucocytic formula develop in a reverse direction and monocytosis sets in.

The number of thrombocytes in the fever period is reduced to between 70,000 and 80,000 per 1^3mm, and goes up to 320,000 per 1^3mm in the recovery period. The duration of the hemorrhage (according to Duke) is 4-6 minutes, a beginning of the blood coagulation (according to Burket) is 3-4 minutes and the end 4-6 minutes. The erythrocyte sedimentation reaction in the febrile period is not high and usually fluctuates between 5 and 15 mm per hour; as a rule, it goes up to 16-70 mm per hour in the afebrile period of the critical stage and during the recovery period.

The clinical forms of hemorrhagic nephrosonephritis. There are 4 basic forms of hemorrhagic nephrosonephritis, according to N. I. Ragoza and G. M. Tsygankov.

1. A toxic infectious form occurring, according to G. M. Tsygankov, in 55% of the cases does not end in death, and is symptomized by general toxi-infectious manifestations accompanied by moderate changes in the kidneys.

2. The nephritic form occurs in 34% of the cases, it is lethal (in about 10%) and characterized by a severe affection of the kidneys developing against the background of hemorrhagic diathesis, pronounced toxicosis, and changes in the nervous system, gastrointestinal tract, and blood.

3. The gastrointestinal or abdominal form occurs in 7% of the cases; it is lethal in 24% and is manifested as an acute infectious entertocolitis, acute gastritis, or even acute abdomen.

The changes in the gastrointestinal tract are symptomized by pronounced toxicosis; hemorrhagic diathesis; affection of the kidneys, nervous system, and blood.

4. The meningo-encephalitic form is observed in 4% of the cases and is lethal in 44%. This form of the disease is symptomized by nephritic, hemorrhagic, and other changes, but the principal forms of the disease are those of meningoencephalitis developing in the second half of the fever period or after the temperature has dropped to normal.

Prognosis. The average mortality in hemorrhagic nephrosonephritis, according to N. I. Ragoza and G. M. Tsygankov, is 5-10%. It should be borne in mind, however, that the prognosis is largely determined by the clinical form of the disease, as the mortality fluctuates from 0 to 44%, depending on the form.

The capacity for work is restored very slowly and the average loss of working per patient is between 3 and 6 weeks.

No residual symptoms are observed after recovery.

Diagnosis. As N. I. Ragoza and G. M. Tsygankov point out, the clinical course of hemorrhagic nephrosonephritis is fairly typical, and that makes it easy to differentiate it from other infectious diseases.

In its initial period (before the appearance of hemorrhagic diathesis) hemorrhagic nephrosonephritis is similar to typhus and influenza.

Indeed, the appearance of the patient, the pronounced manifestations of a generalized intoxication, the involvement of the nervous system in the process and, finally, the petechial enanthema, combine to resemble the picture of exanthematous fever. But the unique epidemiological prerequisites for typhus, its subacute development, the predominance of headaches over all the other complaints, symptoms of stimulation, the early enlargement of the liver and spleen, the absence of the Pasternatskiy symptom, as well as the laboratory data (neutrophilic leucocytosis and monocytosis) and a serological diagnosis, make it possible to distinguish hemorrhagic nephrosonephritis from typhus without any difficulty.

Epidemic influenza, which is still more similar to the initial period of hemorrhagic nephrosonephritis, is ruled out on the basis of a negative Pasternatiskiy symptom, the presence of unique headaches, pain in the arcus superciliaris and the moving eyeballs, and in absence of such intensive pain in the waistline and abdomen as noted in influenza. The difference between the epidemiological data of both diseases and those of a serological diagnosis make it possible to identify the disease with certainty.

In its initial period hemorrhagic nephrosonephritis resembles the anicteric leptospirosis occurring in the Far East. That disease has a number of epidemiological characteristics (it is associated with bathing in ponds, working in marshy fields, peculiar seasonal characteristics, etc.); it is characterized by an early enlargement of the liver and spleen, subicteric sclera, and pain in the musculus gastrocnemius when pressed. The diagnosis is confirmed by the data of a bacteriological investigation and a simultaneous reaction with lysisagglutination.

The clinical picture of hemorrhagic nephrosonephritis during the critical stage is so typical that the disease can be diagnosed without any difficulty. But in cases with prominent gastrointestinal symptoms combined with the muscular protection of the abdomen and leucocytosis, the disease may resemble an acute abdomen developing as a result of a perforative appendicitis, a perforative stomach ulcer, or intestinal obstruction.

Such diseases as an acute infectious glomerulonephritis and a diffuse nephrosonephritis must occasionally also be ruled out.

It is not difficult to pinpoint hemorrhagic nephrosonephritis among other hemorrhagic fevers.

The Crimean hemorrhagic fever differs from hemorrhagic neprhosonephritis primarily by its endemic area (mostly the Far East),

the rising incidence of the disease in wintertime, a less prominent hemorrhagic syndrome (hemorrhages, etc.), leucocytosis in the blood observable during the critical period, and, most of all, the changes in the kidneys.

Unlike hemorrhagic nephrosonephritis, the Omsk hemorrhagic fever is observable in Western Siberia and occurs in the spring-summer-autumn period; the disease is comparatively mild, the hemorrhagic symptoms are less pronounced and leucopenia is noted in the blood.

It is characteristic that the changes in the kidneys produced by the Omsk hemorrhagic fever are temporary, not profound, and are never accompanied by uremia; a peculiar feature of the disease is the frequent complications in the lungs.

A final diagnosis of a hemorrhagic nephrosonephritis is achieved by a complement-fixation reaction.

Laboratory diagnosis. A laboratory diagnosis of hemorrhagic nephrosoneprhitis can be made by a complement-fixation reaction, neutral reaction, as well as by isolating the virus from the patient's blood.

Of practical importance from a clinical point of view only is the complement-fixation reaction, which is used for finding antibodies in blood of the patients and convalescents and produces positive results after the end of the first week of the disease.

There are indications that the complement-fixation reaction (in cold temperature) can be used for finding antigens in the patient's blood and produces positive results in this case during the first 5 days of the fever.

The virus-neutralization reaction is made with a serum of convalescents or former patients and is important also for a retrospective diagnosis or other research purposes.

The isolation of the virus from the patient's blood or urine is now used for research purposes only and not for a practical diagnosis of the disease.

Treatment. According to the data of A. V. Churilov and S. S. Rotenburg and certain American investigations made in Korea (1953), the serum of convalescents proved ineffective in the treatment of hemorrhagic neprhosonephritis. N. I. Ragoza and G. M. Tsygankov nevertheless believe that sero-therapy is a promising method of treatment. According to S. L. Glazunov (1954), the use of blood plasma from convalescing patients in 7 serious cases of the disease in Kalinin oblast produced good or promising results.

The measures used in the treatment of hemorrhagic nephrosonephritis includes immediate hospitalization of the patients, confining them to bed, and keeping them on a vitamin-rich light dairy and vegetable tiet. Daily treatment of the oral cavity and nasopharynx is also required.

An intravenous introduction of ascorbic acid, a 10% solution of sodium-chloride, and an injection of vitamin K are recommended for reducing the hemorrhagic diathesis.

A large intake of liquid and intravenous injection of glucose combined with insullin injections should be prescribed against acidosis and intoxication.

These measures also prevent the development of dehydration.

Narcotic and bromides should be used against persistent vomiting. Camphor, caffiene, and ephedrine are used for improving the tonicity of the cardiovascular system.

Baths taken in 38° water temperature are helpful against general toxic and uremic manifestations, as well as persistent pains. The development of uremia calls for continued glucose-insulin therapy and may require some blood-letting.

Intravenous injections of a 10% solution of calcium chloride in 10 ml doses are helpful in case of anuria.

Oxygen therapy (500-600 cm^3) may be helpful, in addition to blood-letting and glucose-insulin therapy, in case uremia is accompanied by the development of a meningo-encephalitic picture.

The glucose-insulin therapy should be continued in the recovery period when polyuria develops and thirst persists; the patient should be confined to bed and continue his dairy and vegetable diet, but the total food and calorie intake may be increased.

In the toxic infectious form of the disease, confinement to bed should last 10-12 days after the temperature has dropped; in the gastrointestinal form, 12-13 days; and in the nephritic form, 20 days and more (N. I. Ragoza, G. M. Tsygankov).

Phrophylaxis. In case of an outbreak the patients should be isolated and hospitalized. The people surrounding the patient should be under observation for 20 days. If the disease is discovered among people living in a camp, it is advisable to move the camp to a place free from rodents.

The prophylactic measures should be designed to fight rodents and protect people from contact with rodents and their parasites.

The measures to be taken against the rodents should include the extermination of various types of field voles, field and forest mice, as well as household rats and mice whose participation in the transmission of the virus to man is assumed by a number of researchers.

The measures designed to protect the population from contact with rodents and their ectoparasites under field conditions include:

1) the selection of camping sites not inhabited by rodents;
2) the destruction and poisoning of the rodents' burrows;
3) the selected camp sites should be cleared of weeds, grass, underbrush, wind-fallen trees, etc.;
4) a ditch should be dug around the camp;
5) keeping the foodstuffs in places inaccessible to rodents;

6) the treatment of the area with DDT or hexachlorane;

7) the treatment of the exposed body areas with tick and insect repellants (dimethyl phthalate).

Specific prophylactic measures against hemorrhagic nephrosonephritis have not been developed.

COMPARATIVE CHARACTERISTICS OF HEMORRHAGIC FEVERS

Characteristic / Name	Omsk hemorrhagic fever	Crimean hermorrhagic fever	Hemorrhagic nephrosonephritis
1	2	3	4
Agent	Filtrable virus; well cultivable on chicken embryos. Susceptible to the disease, in addition to man, are many types of mammals. The white mouse is an experimental model.	Filtrable virus; methods of its cultivation still inadequate. Susceptible, in addition to man, are monkeys, cats, young rabbits and possibly mice.	Filtrable virus; methods of its cultivation still inadequate. There is no reliable experimental model.
Epidemiology	The disease is endemic to the rural areas of the Omsk and Novosibirsk oblasts (Large Baradinskaya Steppe). Dermacentor pictus and Dermacentor marginatus ixodic ticks are both the reservoir and carriers of the infection. The infection is produced by the bite of an infected tick.	The disease is endemic to the rural areas of the Crimea & Central Asia. It occurs in the Astrakhan oblast, Moldavian SSR, as well as Bulgaria The Hyalomma plumbeum ixodic tick is the reservoir and carrier of the virus. The infection is produced by the bite of an infected tick	The disease is endemic to the rural areas of the Far East, Northeast China, and Korea; occurs in the Yaroslav and Kalinin oblasts. The Gamasidae-type ticks and, possibly, rodents are the reservoir of the virus The infection is probably produced by contact with the excrements of sick rodents and the bites of Gamasidae-type ticks and fleas.

Name / Characteristic	Omsk hemorrhagic fever	Crimean hermorrhagic fever	Hemorrhagic nephrosonephritis
1	2	3	4
	Season: spring-autumn period.	Season: spring-summer period	Season: all year round with maximum activity in summer-autumn period (Far East).
	A stable immunity develops after recovery from disease.	A stable immunity develops after recovery from disease.	A stable immunity develops after recovery from disease.
	The patients are not dangerous for the surrounding people.	The patients are not dangerous for the surrounding people.	The patients are not dangerous for the surrounding people.
Incubation period	2-7 days	3-7 days	11-23 days (an average of 15 days)
	Acute onset. Duration of fever period 5-15 days. A second fever wave occurs in 40-50% of cases after the temperature has dropped to normal.	Acute onset. Duration of fever period 5 to 15 days. Two-hump temperature curve observed in 80% of the cases.	Acute onset. Duration of fever period 4-9 days. Occasionally a second fever wave occurs after temperature has dropped to normal.
Clinical picture	Initial period lasts 3-4 days and is characterized by fever and general toxic manifestations.	Initial period lasts 5-6 days and is characterized by fever and general toxic manifestations.	Initial period lasts 2-4 days and is characterized by fever and general toxic manifestations.

Name / Characteristic	Omsk hermorrhagic fever	Crimean hemorrhagic fever	Hemorrhagic nephrosonephritis
1	2	3	4
	Hypermia of face and upper half of body, hyperemia of pharynx, blood in sclera vessels, occasionally enanthema in pharynx.	Hyperemia of face and neck, hyperemia of pharynx.	Hyperemia of face, neck, chest and upper extremities, blood in sclera vessels.
	No clear changes noted in internal organs.	No clear changes noted in internal organs.	No clear changes noted in internal organs.
	Tendency to relative bradycardia.		Relative bradycardia. Typical pains in waistline and positive Pasternatskiy symptom.
			Severe cases reveal indications of an affected central nervous system (symptoms of meningism).
	Blood picture: developing leucopenia with moderate neutrophilia with nuclear shift to left; mild thrombopenia.		Blood picture: leucopenia with stabnuclear shift of neutrophils, aneosinophilia.

Name / Characteristic	Omsk hemorrhagic fever	Crimean hemorrhagic fever	Hemorrhagic nephrosonephritis
	Critical period begins on 3rd-4th day of the disease with symptoms of hemorrhagic diathesis. The patient's condition becomes aggravated. A mild, punctal petechial rash, occasionally a roseolar rash, breaks out on 3rd-4th day of the disease. Noted also is nasal, gastro-intestinal, pulmonary, and uterine bleeding. Characteristically, the hemorrhagic syndrome is considerably less pronounced than in the other types of hemorrhagic fever. A relative bradycardia is observed; moderate changes in the heart and vascular hypotonia. A characteristic feature is the frequent (in about 3 of the patients) affection of the lungs in the form of specific broncho-pneumonia. The liver and spleen are not usually enlarged.	Critical period begins on 3rd-6th day of the disease with symptoms of hemorrhagic diathesis. Temperature begins to go down at the same time. The patient's condition becomes aggravated. A characteristic enanthema appears in the patient's pharynx and a rash on the body between the 3rd and 6th day of the disease; the rash is petechial (in severer cases) or roseolar (in milder cases), it is light and localized on lateral surfaces of chest, on internal shoulder surfaces and, less frequently, in subclavicular and supraclavicular areas. Developing nosebleeds, bleeding oral cavity, blood vomiting and intestinal bleeding. Hemorrhages in the lungs, kidney parenchyma and pelvis are observed as well as uterine and aural bleeding.	Critical period (fever stage) begins between 3rd and 5th day of disease with symptoms of hemorrhagic diathesis; patient's condition becomes aggravated. From the 3rd or 5th day of the disease the high temperature and intense intoxication are accompanied by a petechial rash localized primarily on the lateral surfaces of the body and in the brachial area; enanthema is found in the pharynx. Nose and gum bleeds are noted. The hemorrhagid syndrome is less pronounced than in the Crimean hemorrhagic fever. There is a characteristic relative bradycardia. No substantial changes occur in the respiratory organs. Vomiting, hiccuping and severe abdominal pains are noted. The liver and spleen are not enlarged. Distinct pathological changes in the kidneys: severe pains in the loin, a positive Pasternatskiy symptom, oliguria, albuminuria and hematuria;

Name / Characteristic	Omsk hemorrhagic fever	Crimean hemorrhagic fever	Hemorrhagic nephrosonephritis
	Kidney changes occur in 20% of the patients, but they are not very profound and appear in the form of infectious toxic nephropathy; no nephritic insufficiency is observed. There are moderate changes in the nervous system (painful syndrome, meningeal symptoms).	The hemorrhagic syndrome is more intensive than in the Omsk hemorrhagic fever or hemorrhagic nephrosonephritis. Characteristic in this case are a relative bradycardia and vascular hypotonia. The respiratory organs are seldom affected. The liver and spleen become enlarged in 20-25% of the cases. Kidney changes are found in the great majority of patients, but they are not profound and appear in the form of infectious toxic nephropathy, no nephritic insufficiency is observed. Changes in the nervous system are noted.	special vacuolized cells, and occasionally the first "fibrinous" cylinders, appear in the urine at the end of this period. Meningeal symptoms are found in the nervous system in some of the cases.
	Blood picture: leucopenia with moderate neutrophilia and nuclear shift to the left; mild thrombopenia.	Blood picture: a typical hypochromic anemia; distinct leucopenia, neutropenia with a sharp stabnuclear shift, relative lymphocytosis, aneosinophilia, occasional monocytosis; a pronounced	Blood picture: moderate hypochromic anemia, leucocytosis, moderate neutrophilia with a "motely" shift, lymphopenia, thrombopenia.

Name / Characteristic	Omsk hemorrhagic fever	Crimean hemorrhagic fever	Hemorrhagic nephrosonephritis
1	2	3	4
		thrombopenia frequently develops; accelerated erythrocyte sedimentation reaction.	Critical period (of the afebrile stage) is characterized by an aggravated condition of the patient and the development of profound kidney changes under normal temperature. Severe pains in the loin and a positive Pasternatskiy symptom; oliguria, reaching the stage of anuria, and a pronounced albuminuria. Small quantities of leucocytes, hyaline cylinders, and erythrocytes are found in the urine sediment. Characteristic is the appearance of large epithelial "vacuolized cells" and special "fibrinous" cylinders. Symptoms of uremia develop (residual nitrogen reaches 60-150 mg%) The cardiovascular system reveals: bradycardia, vascular hypotonia, indications of an affected heart muscle. No substantial changes in the lungs. Gastrointestinal tract: abdominal pain, vomiting,

Name / Characteristic	Omsk hemorrhagic fever	Crimean hemorrhagic fever	Hemorrhagic nephrosonephritis
1	2	3	4
			nausea and hiccuping. The liver and spleen are not enlarged. Blood picture: normal or slightly increased number of leucocytea, monocytosis, accelerated erythrocyte sediment reaction.
Mortality	1%	3%	5-10%
Laboratory diagnosis	Complement-fixation reaction, used for discovering antibodies, produces positive results after the end of the first week of the disease.	Complement-fixation reaction, used for discovering antibodies, produces positive results after the first week of the disease.	Complement-fixation reaction, used for discovering antibodies, produces positive results after the first week of the disease.
Treatment	The serum of convalescents, symptomatic therapy.	The serum of convalescents, symptomatic therapy.	Symptomatic therapy.
Prophylaxis	Measures to fight carrier-ticks. Active vaccination against Omsk hemorrhagic fever.	Measures to fight carrier-ticks. Active vaccination against Omsk hemorrhagic fever.	Measures to fight rodents and protect people from contact with rodents and their parasites.

ROCKY MOUNTAIN SPOTTED FEVER

Definition. The Rocky Mountain spotted fever is a unique acutely febrile disease of a richettsial nature, endemic to the American continent and characterized by natural foci. Rocky Mountain fever belongs to a spotted fever group which includes also such diseases as Marseilles fever, North Asian tick-borne spotted fever, vesicular rickettsiosis, and certain other diseases which have a number of common features and are transmitted by ixodic and Gamasidae-type ticks.

History. Known to doctors for a long time, the Rocky Mountain spotted fever was first described in 1899 by the American researcher Maxey, who referred to its infectious etiology.

Between 1906 and 1909 that disease was studied in detail by Rickets, who isolated the causative agent and established the role of the Dermacentor andersoni tick in its transmission.

A detailed study of the agent's morphology, as well as the pathomorpholy of this rickettsiosis, was made in 1916-1919 by Wolbach.

At the end of the 1920s Parker and Spencer used infected ticks to develop a vaccine against the American spotted fever. An egg vaccine eventually developed by Cox is now being used on a large scale in the U.S.

Etiology. The causative agent of the Rocky Mountain fever is a special type of rickettsia, Ixodoxenus ricketts, or as it is frequently called in literature, Rickettsia rickettsi (Brumpt, 1927), representing typical intracellular parasites which, like the other types of spotted tick fever, are capable of affecting not only the cytoplasm but also the cell nucleus (Wolbach, 1919).

The agent of the Rocky Mountain spotted fever belongs to the Rickettsia family. That family includes the rickettsia whose original hosts were the ixodic ticks. The best known types of rickettsia have now developed into parasites within the organisms of warm-blooded animals and some of them have become parasites of new types of insects, fleas, and lice (V. M. Zhdanov, 1953). V. M. Zhdanov classifies the Rickettsia family into 3 subspecies: Rickettsia, Ixodoxenus, and Gamasoxenus. The Rickettsia supspecies is the youngest evolutionary branch consisting of the 2 causative agents of epidemic and endemic typhus. The Ixodoxenus subspecies is an older phylogenic branch which gave rise to the Rickettsia subspecies (V. M. Zhdanov, 1953). The representatives of the Ixodoxenus subspecies are the primary parasites of ixodic tick which is indicated by the fact that they are found in the deeper tissues of the arthropods and by their ovarian transmission of the virus, whereas the Rickettsia subspecies is found primarily in the insect's intestine.

The morphologically described microorganisms are characterized by a considerable polymorphism; they represent a bacilliform homogenous

structure -- small bacilli with inclusions of chromatin and double lanceolate forms somewhat resembling small pneumococci. When localized, concentrations of tiny formations are revealed in the nuclei. The size of the causative agent varies from 200 mμ to 1 μ ; the agent cannot pass through bacterial filters.

The rickettsia of the Rocky Mountain spotted fever, just like all the other rickettsia, are gram-negative. When colored by the Romanovsky-Giemsa method, they take on a violet hue; the Castened method produces a light blue color, and the Machiavelli method a red color. It may be assumed, by analogy with other types of rickettsia, that the same color can be produced also by the Zdrodovskiy method. The latter method may be briefly described as follows: a thin layer of the material is spread over a glass, dried in the air and fixed over the flame of the burner. Diluted carbolic fuchsin is then poured over the preparation and is used for coloring in the course of 5 minutes. The preparation is then washed off with water and rapidly differentiated (1-3 seconds) by immersing it in a vessel with a mild solution of one of the organic or mineral acids listed below (0.15% solution of acetic acid; 0.5% solution of citric acid; 0.5 % solution of tartaric acid; 0.01% solution hydrochloric acid). The preparation is then washed with water again and colored for 10 seconds with a 0.5% solution of methylene blue. The preparation is then washed a third time with water and dried with filter paper. By this method the rickettsia, as has already been pointed out, take on a ruby-red color and the cellular elements a light blue or blue.

The antigenic structure of the American spotted fever rickettsia is complicated. Agglutination and complement-fixation reaction, as well as tests on the cross-infection of recovered guinea pigs, reveals an antigenic relationship between the agent of the Rocky Mountain spotted fever and the rickettsia of the Marseilles fever (Ixodoxenus conori) and the North Asian tick-borne typhus (Ixodoxenus sibiricus). The Rocky Mountain fever agent can be differentiated from them only by the titer. The spotted fever rickettsia have common antigens with X_{19} and X_2 proteus and less often with X_K.

The agent, just like the other representatives of the rickettsia group, does not grow in artificial nutritive media without a living tissue, but it can easily be cultivated on live and infected tissues (Carell tissue cultures and Cinsser serumal agar), as well as on a chorioallantoic membrane and in yolk sacs of developing chicken embryos. The latter die on the 4th-5th day after the infection.

Ixodoxenus rickettsi are not very resistant to unfavorable affects of the external medium: when heated to 50° they die within a few minutes; when dried at room temperature they are dead within a few hours. At room temperature the blood of a sick guinea pig remains contagious for 1 week, and in a refrigerator for 2 weeks. The agent is no less sensitive to the affect of ordinary disinfectant solutions (Cox, 1952).

To preserve the virus, it is recommended that the brain or spleen suspension of the infected animals be kept in chemically pure glycerin in sealed ampules at low temperatures (dry ice). Under such conditions the agent can retain its effectiveness up to a year.

Of the experimental animals, guinea pigs are the most sensitive to the rickettsia of Rocky Mountain fever; they can be infected both by the parentarel introduction of virus-containing material and by the bites of infected ticks. It should be borne in mind, however, that, depending on the virulence of the virus strain, the clinical picture may vary from an asymptomatic course to forms ending in the death of the animals. In the case of a pronounced infection caused by the bite of a tick, the incubation period fluctuates on the average of from 3 to 7 days, and in the case of an intraperitoneal introduction of infected blood from 2-5 to 6-10 days. The duration of the incubation period depends primarily on the virulence of the strain. The fever attack following the incubation period lasts 7-10 days, during which the temperature curve remains at a 40-41° level. One of the first symptoms of the American spotted fever in male guinea pigs is a swelling and reddening of the scrotum appearing on the 3rd-4th day of the fever regardless of the method of infection. The scrotal reaction may be accompanied by necrosis in the formation of scabs.

It should be borne in mind that the scrotal phenomenon may be absent during the introduction of certain strains. Necroses and scabs are frequently observed also on the legs andears of the sick animal.

The mortality of the guinea pigs infected with the rickettsia of Rocky Mountain fever may fluctuate from 0 to 50-100%. The recovered animals acquire a stable immunity to later infections.

A pathohistological investigation of the animals which died or were killed during the critical fever stage establishes the presence of thrombonecrotic endangiitis. The rickettsia are found primarily in the endothelial and muscular cells of the affected vessel areas.

The blood or an emulsion of the animal's spleen taken during the critical fever period is ordinarily used for further tests.

Though little susceptible to the causative agent, rabbits may also reveal a scrotal reaction and aural necroses.

When infected by ordinary methods, rats and mice go through the disease without symptoms. In the case of intranasal infection, the mice develop a specific pneumonia with an accumulation of rickettsia in the lung tissue.

The clinical picture of the Rocky Mountain fever in monkeys resembles that of the disease in man and may be accompanied by a characteristic rash.

Epidemiology. Before the end of the 1920s it was believed that the Rocky Mountain spotted fever was confined only to the mountains of the north-western areas of the U.S. But in later years the outbreak of the disease was recorded also in a large number of other places. Moreover, certain diseases long since occurring in certain countries of

South American and described by various local names, also proved to be the spotted fever. The Tobia fever in Colombia and the Minas-Geraes exanthematous typhus in Brazil, etc., may be cited as examples. The prevalence of endemic foci of spotted fever can now be described as follows:

In the United States, cases of the disease have been recorded in almost all states with the exception of Maine and Vermont.

In Canada the sources of the disease are found in British Columbia, Alberta, and Saskatchewan provinces.

Spotted fever occurs also in the western and central parts of Mexico, in Brazile (Sao Paulo, Rio de Janeiro, and Minas-Geraes states), in Colombia (Cundinamarca, Santander) and probably in Venezuela.

The annual incidence of spotted fever is comparatively low. The average number of cases recorded annually in the U.S. is about 500. Six hundred and sixty-three cases of the disease were diagnosed in Brazil between 1929 and 1942, and only 12 cases in Canada in 20 years (1919-1939).

The location of the reservoir of the virus in nature among mammals still remains an open question. It may be assumed that certain wild rodents serve as a reservoir and source of infection for ticks. This is confirmed by the fact that most of the rodents in North America are susceptible to the agent of the Rocky Mountain fever. Moreover, an immunity to the infection is found in certain rodents (squirrels, marmots). This shows that they have gone through a certain form of the disease caused by this agent. The assumptions that the reservoir of the virus is found among mammals justify the experiments designed to determine the sensitivity of certain animals to the causative agent of the spotted fever. Thus the investigations carried out in Brazil showed that dogs are not only sensitive to the infection by the spotted-fever agent but are also infected under natural conditions. The same investigations established the natural infectivity of opossums. Complement-fixing antibodies with respect to spotted fever rickettsia were revealed by a titer test in dogs, foxes, and raccoons in New York state. Of some interest is the fact that the dissemination of spotted fever in the U. S. corresponds exactly to the zone inhabited by a certain type of gray rabbits. Worthy of attention among the other North American mammalian animals presumed to maintain the infection are the tree squirrel, snow rabbit, the large North American hare, the chipmunk, marsupial rat, forest rat, meadow mouse, cervine mouse, weasel, and marmot. Until recently, however, naturally infected animals were not found in the U.S. Only once was the virus of the spotted fever rickettsia isolated from a marsupial rat, but it was lost before there was a chance to study it in detail. Moreover, Gauld and Meissa (1954) isolated a rickettsial strain from one of 65 meadow mice and identified it as the causative agent of the Rocky Mountain fever after a thorough investigation.

The source of the infection may reside also in certain agricultural animals. For example, a mild rickettsial infection can be reproduced by infecting sheep.

Thus the range of the mammalian animals suspected to be the reservoir of the spotted fever virus is very wide. Experiments have shown that the majority of the presumed hosts, when infected with Rocky Mountain fever rickettsia, go through an asymptomatic infection without any visible pathological changes or temperature reactions but retain the agent in their organism for a long time.

The bite of a carrier tick is the principal cause of human infection under natural conditions, but the possibility of contracting the disease through the contact of infected material (for example, the liquid of crushed ticks) with the mucous membrane or skin should not be excluded. Experiments with animals have shown that the infection can take place when the rickettsia comes in contact with the conjunctiva or even with uninjured skin (Spencer and Parker, 1930).

The excrements of the ticks also contain rickettsia, but the latter are apparently considerably less virulent than those contained in the tissues and are incapable of causing the disease when coming in contact with uninjured skin. Dried excrements rapidly lose their infectivity, and the infection by such materials through the respiratory tracts, as is the case in typhus, is not very probable.

The transmission of the agent from man to man has not been observ... and the patient is therefore not dangerous for the surrounding people.

Ticks are the principal natural reservoir of the virus for this type of rickettsiosis in view of their capacity to transmit the agent to their progeny and retain the virus for years.

In view of the fact that the ticks are both the reservoir and carriers of the virus, the epidemiology of the Rocky Mountain spotted fever is, in the final analysis, determined by their biological characteristics. The circle of ticks participating in the dissemination of spotted fever is fairly wide and varies according to the geographical location of the focus. This also involves a change of certain epidemiological patterns. The carriers of the American spotted fever under natural conditions are various types of ixodic ticks. People are usually attacked by the adult ticks.

The most important carriers in the western and northern states of the U. S. are the Dermacetroxenus andersoni forest ticks, and in the northern states the Dermacentroxenus variabilis dog ticks. The epidemiology varies accordingly. Thus in the western states the majority of cases are recorded in April-May when the Dermacentor andersoni are most active. The highest incidence in the eastern states occurs in the summer. The majority of the patients in the west are adult males (forest rangers, geologists, hunters, etd.) who are most frequently attacked by the Dermacenter andersoni ticks whose habitat is far from inhabited points. Cattlemen are also subject to the disease, as this type of adult ticks parasitize domestic animals found in pastures. In

the east the professional composition of the patients is entirely different, with women and children accounting for an increasing number of cases. This is explained by the fact that the Dermacentor variabilis ticks also live on dogs.

The following ticks, in addition to the above-mentioned, were found to be spontaneously infected in the U.S.: Amblyomma americanum, Amblyomma maculatum, Amblyomma cajennense, Dermacentor occidentalis, Ixodes dentatus, Rhipicephalus sanguineus. Moreover, the infection can be spread among wild rabbits by the Ahemophysalis leporis palustris ticks which do not attack people. The infected animals, in turn, become a reservoir which is then used as a source of infection by the larval forms of Dermacentor andersoni and variabilis ticks (Parker, Pickin, etc., 1951).

In Canada the carrier is the Dermacentor andersoni tick; in Brazil the Ablyomma cajennense, Amblyomma ovale, Amblyomma brasiliensis, and Amblyomma cooperi; in Colombia the Amblyomma cajennense, in Mexico Rhipicephalus sanguineus, and Amblyomma cajennense.

The capacity for transmitting the disease was proved, in experimental conditions, also in the case of a number of ixodic and certain argus ticks.

Thus the epidemiology of the Rocky Mountain spotted fever fully justifies its classification in the group of the natural-fucus diseases.

A characteristic epidemiological feature of the spotted fever is its different degrees of severity in different source areas. For example, in Montana the average mortality among adult patients amounted to 80%, whereas in Idaho it did not exceed 5%. The difference in the severity of the disease revealed in various source areas of the U.S. led American researchers to the conclusion that 2 geographically differentiated forms of spotted fever exist in the U.S.: a malignant western form peculiar to the northern and western areas with the Dermacentor andersoni tick as the major carrier, and a benign eastern form occurring in the eastern and central states. But the latest information shows such view to be erroneous. Lengthy observations of the foci of infections showed that the severity of the diseases is subject to considerable changes. In the above-mentioned source area in Idaho (western U.S.), the mortality rate of spotted fever in previous years did not exceed 5%, but later rose to 25-35%, that is, the benign source developed into a malignant one. A comparison of the mortality figures between the western and eastern areas showed that there is almost no difference between the average indexes. This also emphasizes the error of dividing the disease into 2 geographic forms.

The recovered patients acquire a more or less permanent immunity to recurrent infections.

Pathological anatomy. Vascular disruptions are the principal pathoanatomical changes caused by Rocky Mountain fever.

Macrascopic investigations reveal hemorrhages in the skin and subcutaneous tissue which are characteristic of this disease. Large-scale hemorrhages in the scrotal tissues accompanied by necrosis in a number of cases, are frequently observed in males. Similar affections are found in the testicles and appendix testis. The spleen is always condensated and enlarged several times compared to its normal size. The inguinal and axillary lymph nodes are enlarged and hyperemic.

A histological investigation reveals a swelling and proliferation of the endothelium, occasionally accompanied by an intravascular proliferation; a pronounced endothelian necrosis and the formation of thrombi are observed, as well as a cellular infiltration and necrosis of the walls of the precapillary rete, particularly the arterial. The following symptoms may be added to the above-listed changes: perivascular infiltration and the formation along the vessels of nodal-type infiltrates consisting of lymphoid, plasmatic cells, and macrophages or primarily of lymphocytes or plasmatic cells. The above-described affections of the vessels are subject to considerable variations, depending on the location and phase of the infection.

Thus the vascular changes in case of Rocky Mountain fever are actually not different from the similar vascular changes in exanthematous fever. Characteristic only is the severity of the affection and the tendency to the formation of necrosis of the vascular wall. The vascular changes frequently result in the formation of obturating forms of necrotic panarteritis or thrombaarteritis which in turn result in necrotic changes of the skin, pelvis, concha auriculae, and fingers. An analogical infection of the arterials is associated also with the formation of microinfarcts in the brain which are particularly characteristic of this type of rickettsiosis.

The clinical picture. The severity of the Rocky Mountain spotted fever may vary from very mild dispensary-treated forms of the disease to malignant cases ending in death.

The incubation period lasts on an average from 6-7 days. But it can also last 2-3 days and, on the other hand, as long as 2 weeks. A short incubation period is typical of the severe forms of the disease (Parker, 1938).

The disease usually begins with severe and sudden chills, a severe headache, pain in the bones, muscles and joints, vomiting, nosebleeds, and rising temperature. In some cases, however, the critical period is preceded by a few days of general indisposition with the patient complaining of slight chills, weakness, and lack of appetite.

The average duration of the fever period is 2-3 weeks, but it may be shorter or longer. In mild cases the temperature increase (to 39°) is more gradual, and it remains at that level. Severe cases are characterized by a higher fever (40°-41°) and a steep rise of the temperature curve. A morning temperature drop of 0.5-1.5° is usual for the Rocky Mountain fever. The fever ends with an accelerated

(3-4) days or protracted (7-8 days) lysis usually occurring at the end of the 3rd week of the disease, and in mild cases at the end of the 2nd week (Figure 5).

In the case of Rocky Mountain fever the primary affect on the spot of the tick bite, characteristic of other types of tick-borne rickettsiosis, is absent. A regional adenitis, however, may be noted in some cases.

A characteristic symptom is a rose-red rash of a macul-papular nature breaking out on the 3rd-4th day of the disease. The rash becomes increasingly pronounced from day to day, and in most cases, with the exception of the mildest forms, acquires a hemorrhagic nature. The rash first appears on the ankles and wrists and then rapidly spreads throughout the body, covering the palms of the hands, the soles of the feet, the scalp, and occasionally also the mucous membranes of the mouth and pharynx. The skin of the abdomen is last and least affected. Gangrenous infection of the skin and mucous membranes may develop in cases of a pratracted disease. During the recovery period the rash becomes pigmented, and furfuraceous desquamation is noted in its heaviest areas (Figure 6).

A relative bradycardia is observed in the cardiovascular system in mild cases, and a sharp increase in pulse frequency (up to 160 beats per minute) in severe cases.

The lungs are usually not involved in the process.

Frequent constipation is noted in the gastrointestinal tract.

The liver and spleen are enlarged. Symptoms of jaundice are frequently noted.

Pronounced changes are noted in the nervous system. Typical of them are severe headaches (especially frontal and occipital). The patients may remain conscious even in lethal cases, but death is usually preceded by a state of delirium or stupor. A neurological examination may reveal the presence of pathological reflexes and skin hyperasthesia. The frequent occurrences include a paralysis of the cerebrocranial nerves, paraplegia and hemiplegia, a deterioration of the eyesight and hearing, and mental disorder. These symptoms may persist for several weeks and even months and then usually disappear without a trace. There are indications, however, that in some patients the lethal outcome of the disease was caused by neurological complications.

An analysis of the boold does not reveal any characteristic changes. Leucocytosis may occur in addition to leucopenia symptoms. In most cases the number of leucocytes does not exceed 15,000 per cubic mm, but it can also go up to 30,000 per cubic mm.

The only changes in the urine are symptoms of albuminuria.

Recovery is slow even in mild cases. Complete recovery takes several months and sometimes even a year and more.

Complications. Complications in Rocky Mountain spotted fever are not uncommon and may vary considerably. Principal among them are pneumonia, hemorrhages (intestinal, nephritis), phlebitis, nephritis, the above-mentioned hemiplegia and paraplegia, and iritis. Necrosis of the skin, especially in the area of the sex organs, is noted in the pratracted diseases.

Prognosis. The prognosis of the Rocky Mountain spotted fever varies according to the clinical forms of the disease and is to some extent connected with the peculiar features of the endemic sources. As a result of this, the mortality rate (prior to the use of antibiotics) was subject to considerable fluctuations, varying from 5-10% to 80%. The prognosis is more favorable in the case of children. The mortality rate among children does not exceed 37.5% even in the areas of the most malignant forms of the disease. The use of antibiotic therapy on time assures a favorable outcome in almost all cases of the disease.

Diagnosis. A clinical diagnosis of Rocky Mountain spotted fever is frequently complicated, prevailing opinion to the contrary notwithstanding. The disease frequently remains undiagnosed in mild as well as in severe and fulminant cases. The diagnosis is particularly complicated in areas where murine typhus also occurs; these 2 diseases should be differentiated to begin with. A comparison between the clinical picture of the Rocky Mountain fever and that of the tick-borne North Asian typhus also points to the presence of a large number of common features. Laboratory investigation methods are used in addition to the clinical and epidemiological data which are taken into account for diagnostic purposes.

Laboratory diagnosis. The most accurate as well as the most complicated method of a laboratory diagnosis of Rocky Mountain fever is the isolation of the causative agent from the patients; this is achieved by an intraperitoneal infection of male guinea pigs. The patients' blood, introduced in 1-3 ml doses can be used as an infective agent. The best results are obtainable by the introduction of whole blood citrate, but coagulated blood, serum and plasma can also be used successfully. The picture of experimentally infected animals may vary considerably depending on the gravity of the disease. Thus the infection of guinea pigs with the blood of seriously ill patients produces a sharply pronounced scrotal phenomenon with necroses of the scrotum; on the other hand, if the blood of mildly ill patients is used for the infection, the scrotal reaction may be mild or absent altogether. A similar relationship is noted in the temperature reaction. In doubtful cases the diagnosis can be confirmed by serological reactions with the blood plasma of recovered guinea pigs and by known rickettsia strains or by a repeated infection with known virus strains.

The value of the Weil-Felix reaction in diagnosing Rocky Mountain spotted fever is highly relative, as it is positive only in serious and moderate forms of the disease and remains negative in mild forms. Moreover, this reaction cannot be used for differentiating spotted fever from exanthematous fever; in positive cases it merely indicates that the disease is one of the rickettsiosis group.

At least two blood tests should be made in the case of a Weil-Felix reaction -- one as soon as spotted fever is suspected, and another between the 12th and 15th day after the onset of the disease. This makes it possible to observe the increasing agglutination titer. Titers above 1:320 are of diagnostic importance. The patients' serum agglutinates the strains of the X_{19} and X_2, the former strain being most frequently agglutinated in larger dilutions than the latter. A reverse interrelation, however, is not excluded (Parker, 1938).

A neutral reaction is undoubtedly more important from a diagnostic point of view than a Weil-Felix reaction as it points unerringly to the presence of spotted fever revealing any form of the disease, including the mildest.

The gist of the reaction is the introduction of a dilution of the test serum in a mixture with a standard strain into the guinea pigs. A mixture of normal serum with the infective material is introduced into the test animals. The serum of the patients possesses neutralizing properties, and when diluted to a certain degree it protects the animals against the development of an infection.

This reaction produces the most permanent results in the recuperation period but the serum of some patients is found to possess protective properties even during the period of falling temperature.

A complement-fixation reaction with the use of a standard specific antigen against rickettsia has been employed successfully in recent years for a serodiagnosis of spotted fever. In view of its high degree of specificity, this reaction can be used for differentiating spotted fever from epidemic exanthematous fever, murine exanthematous fever, Q-fever and tsutsugamushi fever. The complement-fixation antibodies usually appear in the second week of the disease and remain for at least 6-8 years. The presence of group antigens in the following infective agents, however, should be borne in mind: Rocky mountain fever and certain types of tick-borne fever -- Dermacentroxenus conori Marseilles fever, Dermacentroxenus sibiricus, the tick-borne exanthematous fever of North Asia, Dermacentroxenus murinus, and vesicular rickettsiosis; all this complicates their serological differentiation.

Treatment. Until recently the treatment of Rocky Mountain fever amounted to the use of hyperimmune rabbit serum (Topping, 1939), symptomatic medicine and general restorative therapy.

The first reports of the successful use of para-amino-benzoic acid in the treatment of that disease (Rose, Duane and Fischel, 1945)

were published in 1946. The use of that preparation shortened the duration of the fever period and considerably reduced the number of lethal cases; but it frequently caused various types of side reactions which, in turn, complicated its use.

The treatment of Rocky Mountain fever was considerably simplified with the introduction of chloromycetin (synthomycin), aureomycin, and terramycin into practice.

The basic methods of treatment used in this disease are:

a) specific chemotherapy and
b) restorative treatment and symptomatic therapy.

The treatment with chloromycetin is as follows: 4 grams are first introduced into the patient orally (based on 50 mg per kilogram of the patient's weight) and followed up every 4 hours by 0.5 grams or every 8 hours by one gram (Parker, 1954). The use of the antibiotic is continued until the toxinemia disappears, the patient's condition improves, and the temperature drops to a normal level (Parker). Barring complications, a clinical improvement may occur within a day and the temperature may go down in 60-72 hours. In view of the fact that antibiotics should be used for 2-3 days after the temperature has dropped to normal, the average duration of the treatment is 5-6 days. Chloromycetin produces the best results when used in the first week of the disease, but the use of that drug in conjunction with a general restorative therapy is effective also in later stages. Zero point 5 gram of the antibiotic is introduced intravenously every 6 hours into patients in a comatose condition. It is best to introduce it together with a 5% glucose solution. The drug may be introduced into such patients intravenously and through a stomach catheter with a view to maintaining a more stable concentration of it. Still better results are produced by aureomycin (Ross, Schenbach, etc., 1948). This antibiotic is introduced orally on the basis of 25 mg per kilogram of the patient's weight every 4-6 hours (Parker) and is followed by the introduction of milk or semi-liquid food to prevent the nausea frequently produced by that drug.

In the case of persistent nausea or a coma, an intravenous introduction of the antibiotic is recommended. When introduced by this method, the daily dose should amount to 5-10 mg per kilogram of the patient's weight. The usual dose is 100 mg every 6 hours. The use of more than one gram a day is not recommended.

The duration of the treatment with aureomycin is the same as with chloromycetin.

Terramycin produces a powerful rickittsio-static effect. When used in the treatment of Rocky Mountain fever, it produces better results than the above-listed antibiotics. This drug is used orally in the same doses and at the same intervals as aureomycin. The treatment continues until the temperature remains at a normal level for 2 days. The drug is introduced intravenously when the patient is in a coma. A premature stoppage of the treatment may give rise to relapses requiring a repetition of the treatment with antibiotics.

In general restorative therapy particular attention is called to the maintenance of an albuminous and liquid balance, as well as to the proper care of the patient. American researchers who have had much experience in the treatment of Rocky Mountain fever emphasize the necessity of the earliest possible introduction of albuminous substances. The daily diet should consist of 3-5 grams of albumin per kilogram of the patient's weight. If the patient is in a coma, he should be fed by a stomach catheter liquid containing sufficient albumin. Albuminous preparations should be introduced parenterally in case of anemia, adema, or hypoproteinemia. The introduction of albumin on time may prevent a collapse. Anuria and azotemia are used as contraindications when the organism is overloaded with albuminous substances.

Particular attention should be paid to the required intake of liquid. Three to 5 liters of liquid a day should be introduced into patients in a coma revealing a sharp dehydration. A slow intravenous introduction of a physiologic solution is also recommended.

Rocky Mountain fever patients should also be subjected to symptomatic treatment in addition to specific and general restorative therapy.

Anti-tick measures and prophylaxis. The prophylactic measures against Rocky Mountain spotted fever consist in:

1) anti-tick measures,
2) the vaccination of people likely to be exposed to the infection.

The fight against ticks includes:

1) the protection against tick bites,
2) the extermination of ticks in nature.

An effective method of preventing tick bites is a mechanical protection which is achieved by wearing tight clothes (the shirt is to be worn inside the trousers and the cuffs and collar to be tightly buttoned). It should be borne in mind that in the areas inhabited by large numbers of ticks, even the tightest clothes cannot prevent their penetration to the body. The tight clothes should therefore be periodically inspected and any ticks discovered immediately removed.

Insect repellants (dimethylphthalate, dibutylphthalate, etc.) can be used effectively for the prevention of tick bites.

The ticks can be destroyed by spraying or dusting certain areas with DDT and hexachlorane.

Two types of dead vaccines are suggested for vaccination against the Rocky Mountain fever. One vaccine is made from the tissues of infected ticks and the other from the rickettsia raised in the yolk sac of developing chicken embryos. Tests on animals (Lackman, Parker, 1948) and epidemiological practice have shown that the 2 vaccines are about equally effective. The vaccine is introduced subcutaneously 3 times in one ml doses at intervals of 7-10 days. The vaccination is repeated once in the following year with one ml. The vaccination

usually offers complete protection from virus strains of low virulence but is considerably less effective in the case of highly virulent strains; but even in such cases it provides considerable alleviation and reduces the number of lethal cases to zero.

It should be pointed out that as a result of lengthy tests on chicken embryos, Cox succeeded in developing a virulent rickettsia strain. That strain may possibly be used for making vaccines in the future.

TSUTSUGAMUSHI FEVER

Definition. Tsutsugamushi fever, or Japanese river fever, is an acute infectious disease of a rickettsia type, endemic to Southeast Asia and the Southeast Pacific islands. It is spread among people by the bite of the larve of certain types of red ticks and is characterized ny natural foci.

History. Tsutsugamushi fever has been known in the Far Eastern countries for a long time. References to this can be found in ancient Chinese literature. In the 3rd century B.C., Ke-Hung described it as "sha-shi," that is, a disease caused by the bites of small red insects (P. F. Zdorovskiy, E. M. Golinevitch, 1953). The popular Japanese name "tsutsugamushi" also indicates that the population associated the fever with tick bites (mushi means tick).

The first description of the Japanese river rever in modern literature appeared in 1810 and is credited to the Japanese author Hasimoto who designated it by a popular name which eventually came into wide usage. In the European medical literature the reports on this disease were published much later (Belts and Kawakami, 1879).

At the beginning of this century Japanese researchers (Tanaka, Kitasima, Miaima, Okumare, etc.) made a detailed study of the etiology, epidemiology, and clinical picture of the tsutsugamushi fever. In particular, they confirmed the previous assumptions, by experiments with monkeys, that the disease was spread by the red tick larva Trombicula akamushi (Kitasima and Miaima), and proved that the virus can be transmitted through the ovaries (Miaima and Okumare). It was eventually established that the field mice caught in the infection areas were capable of spontaneous infection with the agent of the tsutsugamushi fever, and the reservoir of the virus in nature was thus determined (Hayasi). A study of an experimental infection in animals enabled Nagayo and Ogata to establish the rickettsial nature of the agent.

Certain important facts were established by English and Dutch researchers. It was proved, in particular, that the patients develop agglutinins affecting not the X_{19} proteus but the X_k strain (Fletcher, Lesslar and Leutwait), and also that mice were the most suitable experimental model for the study of that infection (Dinger).

A definite contribution to the study of the tsutsugamishi fever was made by American researchers most of whose efforts were made during the Second World War. The increased interest in the disease during that period was explained by the fact that the American military personnel operating on the Pacific islands had suffered severely from tsutsugamushi fever. Of the 6,685 cases of the disease officially recorded among the American military personnel in the Second World War, 284 were fatal. There was a total of over 20,000 cases of the disease among the Anglo-American tropps. The high incidence of the disease among the military personnel in certain areas can be illustrated

by a large number of examples. Thus after the landing of an American regiment on one of the Southwest Pacific islands, 400 soldiers came down with tsutsugamushi fever. After a 2-months' stay in Burma in 1944, 18% of the personnel of a British battalion came down with the tsutsugamushi fever and 5% of them died (Smadel, 1952). All this forced the American and British researchers to initiate an intensive program designed to develop a treatment and prophylaxis of the tsutsugamushi fever. Certain prophylactic and therapeutic measures were developed by the end of the war.

Etiology. The causative agent of tsutsugamushi fever is a special type of rickettsia, Trobidoxenus orientalis, or as some investigators call it, Rickettsia orientalis. The tsutsugamushi fever agent belongs to the Trombidoxenus type which is represented by the primary parasites of red ticks re-adapting themselves to the organism of war-blooded animals. Genetically, such agents are apparently very closely related to the Rickettsia type, as they are similar to them in their group antigens and in ecology (V. M. Zhdanov, 1953).

Morphologically, the rickettsia of this type are identical with the other agents of the tick group and represent polymorphic coccobacillary or bacilli-form formations of bipolar stain and 0.3-0.5x0.8 mμ size. The rickettsia do not pass through bacterial filters, arrange themselves intracellularly, and do not extend to the nucleus of the affected cells. An extracellular arrangmment, however, is also possible. According to Macciavelli, they take on a red hue. It should be borne in mind, however, that one of the characteristics of tsutsugamushi fever rickettsia is that they are easily discolored when differentiated by a mild acid after coloring them with fuchsin; as a result, the rickettsia and the cells containing them can equally be colored with methylene bluing. Various modifications rather than the original method of coloring should therefore be used for coloring them.

In smears colored by the Romanovskiy-Giemsa method the rickettsia appear as bright violet formations.

The tsutsugamushi rickettsia have a complicated antigenic structure and are serologically clearly separated from the other types. Clearly seen inside this type is a pronounced heterogeneity which is particularly manifested in neutralization tests. The sera developed by the immunization of animals with a certain strain cannot protect them against being infected with a different strain (Bell, Bennet, Whitman, 1946; Bennet, Smadel and Gold, 1947). The causative agent has common antigens with the X_k proteus (Fletcher, Lesslar, Leutwait, 1929).

Used successfully for the cultivation of tsutsugamushi fever rickettsia are developing chicken embryos -- infecting the chorioallantoic membrane and yolk sac of 5-6 day old embryos, as well as the agar-tissue medium developed by Cinsser (Smadel, 1952).

The agent is characterized by considerable lability and little stability in the external environment. It can be inactivated in 10 minutes by heating it to 50°. It rapidly dies in 0.1% formalin and 0.5% phenol.

The infective agent can be preserved for a long time in a 70° temperature. Lyophil-drying, even under the most scrupulously observed conditions, produces only relatively satisfactory result in view of the considerable reduction of the infective titer (Jackson and Smadel, 1951).

First among the susceptible experimental animals are white mice which, being very sensitive to this rickettsiosis, are most frequently used for laboratory investigators. The usual method of infection is the intracerebral introduction of the infective material. The disease in this case develops between the 7th and 8th day after the infection, and the abdomen becomes distended. An edema of the subcutaneous tissue of the abdominal cavity occasionally develops. This is followed by a pronounced dyspnea, and between the 10th and 15th day the animal dies. An autopsy reveals, in addition to the mentioned tissue edema, lymphadenitis, hyperemia of the peritoneum, and serous-fibrinous exudate in the abdominal cavity. The spleen is greatly enlarged and covered with exudative flakes. A characteristic exudate is found also in the pleural cavities. Focal hemorrhagic pneumonia may be found in the lungs. Rickettsia are observed in the preparations made from the exudate and in the smears taken of the affected tissues. They are practically always seen in the smears of the spleen surface or peritoneum. It is recommended that the blood organ emulsion (spleen, liver, brain) of the dead and killed infected animals be used for further passages.

An intranasal infection results in the development of a specific pneumonia.

Hayasi and Sanda (1953) suggest the use of intracerebral passages to maintain the viruses in an active condition. Such passages preclude the possibility of contaminating the virus with the microbes of the animal's intestinal tract which is frequently the case with intra-abdominal infection. An intracerebral infection does not in any way affect the characteristics of the infective agent.

The considerable fluctuation of the virulence of the tsutsugamushi fever rickettsia strains used for mice should be taken into account.

An intraperitoneal injection of rats produces an asymptomatic infection, and the agent can be preserved in the brain for more than 3 months.

An ordinary infection in guinea pigs can be reproduced only by an intraperitoneal injection of adaptive strains. The infection is characterized by a febrile reaction occurring after the incubation period and lasting 3 to 11 days; the duration of the incubation period is also subject to considerable fluctuation (6-12 days). In addition to fever, an intraperitoreal infection develops a specific ascites

with an accumulation of rickettsia. There is no development of a scrotal phenomenon. Mortality depends on the virulence of the strain and may vary within a wide range (from 0 to 90%). An ulceration may appear at the place where the pathogenic material has been introduced intracutaneously.

Characteristic of rabbits is a testicular and ocular form of infection.

Monkeys can be infected both by red tick larva bites and any other method of parenteral introduction of the infective material.

After 6-7 days of incubation the animals develop a fever lasting 5 to 20 days. No rash is observed on the monkeys. The disease is usually mild.

Of all the mentioned sensitive laboratory animals, white mice are used in most cases for isolating and identifying the tsutsugamushi fever rickettsia.

Epidemiology. Tsutsugamushi fever is widespread in the countries of the Far East and the Southeast Pacific (Figure 7).

The sources of the disease have long been known in Japan: they are found in the river valleys on Honshu island. The disease originating there is malignant (the mortality is as high as 30%).

Outside of Japan, sources of tsutsugamushi fever are found also on Taiwan and Penhuletao islands, in Vietnam, Laos, Cambodia, Burma, East India, Ceylon, Indonesia, New Guinea, and Australia.

Tsutsugamushi fever may possibly be found also in the coastal area of Central China and in South Korea (possible sources). It should be pointed out that the gravity of the disease varies according to the geographic location of the source. Thus the mortality rate in Japan is as high as 30%, while in Indonesia it does not exceed 9%. This has prompted certain researchers (V. M. Zhdanov, 1953) to consider the Trombidoxenus orientalis as containing several geographic varieties of the causative agent: Trombidoxenus orientalis var. nipponica; Trombidoxenus orientalis var. indica; Trombidoxenus orientalis var. indonosica; Trombidoxenus orientalis var. australis.

According to these authors, the variants differ by the dissemination area, pathogenicity in man and animals, as well as by the reservoir of the virus, the carriers, and antigenic structure.

Tsutsugamushi fever can be transmitted to man only by the bites of certain types of red ticks.

Mention should be made of a known case of intralaboratory infection with tsutsugamushi fever made possible by introducing the infective material into the conjunctiva (Chao Shu-suan, Chao Chun-fan, etc., 1953). The patient is not dangerous to the surrounding people.

The virus-carriers in Japan, Taiwan, and the Pescadores islands are the Trombicula akamushi ticks; and on the Malayan peninsula, in Burma, East India, Ceylon, Australia, Indonesia, and New Guinea the Trombicula delhiensis ticks. In the last two countries the Trombicula fletcheri ticks are also important from an epidemiological

point of view. Only the larva of these ticks feed on blood, and they alone attack people and animals.

Serving as carriers in their larva stage, the red ticks are the major reservoir of the virus by virtue of their ovarial transmission. Another natural reservoir of the virus are certain types of small rodents (field mice in Japan, wild rats and bendicotes in Australia, etc.) on which the red tick larva feed.

The red ticks thus acquire the rickettsial infection by two methods: by ovarial transmission and by attacking sick rodents; this is confirmed by the isolation of the causative agent from the larva removed from field mice caught in the infection area (Kawamura). But only the larva which acquire the virus ovarially are of an epidemiological importance, as they attack warm-blooded animals only once.

These data justify the conclusion that the epidemiology of the tsutsugamushi fever is the same as that of the Rocky Mountain fever, and is determined primarily by the biological characteristics of its carriers, the red ticks.

The larvae of these ticks live in the damp soil or in the rock waste covering the ground and in the jungle overgrowths. They crawl over the grass in search of blood and attack the people and animals coming in contact with them. The infection areas are therefore clearly outlined. Thus in Japan people can become infected in the uncultivated sections adjoining the river, while 10 meters away, where the land is cultivated, no infections ever occur.

Chinese researchers (Chao Shu-suan, Sui Chao-kui, etc., 1953; Chao Shu-suan, Chao Chun-fan, etc.) produced convincing proof that infected white mice release a large quantity of rickettsia with their urine which makes it highly infective. It has been established experimentally that the causative agent can be transmitted from sich animals also by physical contact, as well by the infective material coming in contact with a lesion.

Mice were known to become infected with the disease when eating the infected corpses of animals. The authors believe that this method of infection can occur also under natural conditions.

Tsutsugamushi fever, like any other communicable disease, is seasonal -- the seasons coinciding with the periods of the carriers' activity. Thus the highest incidence of the disease in Japan occurs in the summer months (July-August), and in the tropics it coincides with the rainy season.

Characteristic also is the occupational element of the patients. Most of the patients in Japan are peasants who visit the carrier-infested places in the summer. Children are mostly affected by the disease on the Penhuletao islands where the carrier-ticks usually breed within the corrals enclosing the residential houses. A large number of patients during the Second World War was found in the units operating in the jungles.

An examination of the principal epidemiological features of the tsutsugamushi fever justifies the conclusion that the disease is a typical endemic rickettsiosis characterized by all the features of a natural focus.

The survivors develop an immunity to the disease, but their insusceptibility to a recurrent infection, which may last many years, applies only to a homologous strain of the virus, that is, a strain with the same antigenic structure that caused the first disease. An infection with a heterological strain may produce a new disease. There are published references to many cases of tsutsugamushi fever arising 1-2 years after a previous infection.

Pathological anatomy. Disseminated focal vasculitis and perivasculitis affecting primarily the vessels of the skin, lungs, myocardium, and brain are the major pathoanatomical changes occurring during tsutsugamushi fever.

It is impossible to establish an specific changes in an autopsy examination. A certain amount of serous-fibrinous exudate is found in the abdominal, pleural, and pericardial cavities. The liver and spleen are somewhat enlarged and hyperemic. An enlargement of the lymph nodes is also noted. Symptoms of bronchopneumonia can, as a rule, be established by an examination of the lungs.

As in most other cases of rickettsiosis, a study of the histological preparations reveals a disseminated infection of the vascular system. The nodules consist of monocytes, plasmatic cells, and lymphocytes. The vascular changes are considerably less pronounced in comparison with exanthematous fever. Necroses and inflammatory changes of the vascular wall, so typical of the Rocky Mountain fever, are absent.

Cut off sections of the parenchymatous organs reveal pathological changes occasioned by the affected vessels. They are particularly pronounced in the heart, lungs, brain, and kidneys. In particular, cardiac-wall preparations always reveal a focal or diffuse interstitial myocraditis of varying degrees. Interstitial pneumonia is found in all lethal cases.

The clinical picture. The incubation period may last from 1 to 3 weeks, but its usual duration is 10-12 days.

The disease is acute from the very onset and is accompanied by chills and a severe headache. The first objective symptoms are an acute hyperemia of the conjunctiva and a moderate enlargement of all the lymph nodes. In some cases a general indisposition, headaches and vertigo, and the loss of appetite are observable in the last days of the incubation period.

Characteristic in this connection is a gradually increasing temperature which usually reaches a maximum (40-40.5°) only at the end of the first week. The duration of the fever period may vary from 2 to 3 weeks, and the falling temperature is of the lysis type (Fig. 8).

An important diagnostic symptom in this type of rickettsioisis is the primary affect which is usually manifested where the clothes adhere closely to the body (around the waist and in the armpits). In the beginning of the fever period it is a concentrated hyperemic nodule with a diameter of about 1 centimeter. At the top of the nodule is a multichamber besicle which become ulcerated in a few days and covered with a dark crust. The ulcer is painless and does not itch. It begins to heal in the third week. The first affect in tsutsugamushi fever is observable in 60-100% of the cases and is, as a rule, accompanied by regional adenitis.

A rash appears on the skin between the 5th and 8th day of the disease. It first appears on the body and later extends to the extremities. The face, the palms of the hands, and the soles are seldom affected by the rash. The rash is of a macular or maculo-papular type, has a reddish hue and disappears under pressure.

Hemorrhages are very rare. The pulse frequency lags behind the temperature and fluctuates between 70 and 100 beats per minute. In serious cases the pulse frequency increases to 120-140 beats per minute in the second week, and the arterial pressure diminishes. A collapse or thrombosis of the vessels and hemorrhages in various localities are possible in severe cases.

A cough develops in the very first week. In the second week of the disease symptoms of bronchopneumonia can frequently be detected by X-ray and physical examination.

The liver and spleen, as a rule, become enlarged.

The disturbance of the nervous system is manifested first of all by headaches which perturb the patient from the very start of the disease and subside somewhat in the second week. Severe cases are frequently accompanied by the development of encephalitis which is symptomized by delierium, stupor, and muscle twitching. According to the American researchers, neurological complications are particularly frequent in the case of persons who had been under nervous strain before the onset of the disease. This was clearly manifested in the study of the disease among the American soldiers who had been in the Pacific theatre of operations during the Second World War. Symptoms of encephalitis were found in about 45% of the cases in that period.

An investigation of the blood during the critical stage of the disease could not reveal any characteristic changes. The number of leucocytes does not exceed the upper limit of the norm as long as there are no complications occasioned by the incrustation of bacterial flora. In some cases there is a tentency to leucopenia in the first week of the disease.

Pathological admixtures indicating the formation of an infectious-toxic nephropathy may be found in the urine.

Recovery begins at the end of the second and beginning of the third week when the falling temperature is indicative of a retarded lysis. The recuperation period is usually quite long.

Prognosis. The prognosis of the disease varies considerably. The mortality rate of the tsutsugamushi fever may fluctuate within a wide range from 1 to 60%. The fluctuations are determined by both the characteristics of the endemic focus and the patient's age. A large number of deaths from tsutsugamushi fever occur among middle-aged people. Death usually comes at the end of the second week of the disease. The causes are a secondary bacterial pneumonia, meningo-encephalitis, and blood-circulation insufficiency. But all this applies to the time when no drugs were available for specific treatment. The prognosis has been considerably changed and mortality practically reduced to nil with the introduction of antibiotics.

Diagnosis. A clinical diagnosis of tsutsugamushi fever frequently involves considerable difficulties in view of the fact that such symptoms as headaches, relative bradycardia, and the absence of leucocytosis which may be observed in a number of other diseases prevalent in the same areas -- dengue, malaria, typhus abdominalis, certain other types of rickettsiosis, etc. The indications of endemic focus in the area found in the anamnesis and the discovery of a primary affect can be used as a starting point for an early diagnosis. Laboratory investigations, particularly a Weil-Felix reaction with a proteic antigen OX_k, are very helpful in diagnosing the disease.

Laboratory diagnosis. The most accurate method of a laboratory diagnosis is the isolation of the causative agent from the patient's blood during the fever period by an intraperitoneal infection of white mice. If tsutsugamushi fever rickettsia are present in the test subjects, the mice will die between the 10th and 18th day after the infection. An autopsy reveals a characteristic picture peculiar to this type of rickettsiosis. A microscopic examination of the smears taken from the spleen surface and peritoneum and colored by the Romanovskiy-Giemsa method reveals tiny violet microorganisms somewhat resembling Diplococci and arranged both within and outside the cells. Peritoneal fluid, blood and a 10% emulsion of spleen, liver, and lung tissues are used for further passages. The final identification is also made in mice by chiasmic serological reactions. When isolating the causative agent in mice, it should be borne in mind that not all the Trobidoxenus orientalis strains bring about the death of the mice in the first passages. Further tests should therefore be made in some cases even when the clinical symptoms of the disease are absent in the animals.

A serological diagnosis of the tsutsugamushi fever boils down to a Weil-Felix reaction with the use of an OX antigen of the Kingsberry proteus strain. The antibodies in the patient's blood serum appear by the end of the second week of the disease, their titer reaches a maximum on the 20th-21st day, and then shows a rapid drop, frequently disappearing $1\frac{1}{2}$ months later. The serum of the tsutsugamushi fever patients produces a positive reaction to the antigen of the X_k proteus and a negative

reaction to the antigen of the X_{19} proteus. A 1:160 dilution of the serum is considered a diagnostic titer, but a single investigation of the serum is of little value and a study of the dynamics of the growing titer is therefore highly recommended.

A complement-fixation reaction cannot be used in view of the large serological variety of the Trombidoxenus orientalis rickettsia strains.

Treatment. Before the introduction of antibiotics the treatment of tsutsugamushi fever was limited to the prescription of symptomatic remedies and general tonic therapy.

The effectiveness of chloromycetin in the treatment of this disease was established by Smadel in 1948. Valuable properties were later found also in two other antibiotics, aureomycin and terramycin (Bailey, Ley, Diercks, etc. 1951).

The American researchers recommend the following dosages: the first dose 3 grams, then 0.5 grams every 6 hours until the temperature is back to normal (Smadel, 1952). The treatment usually last 24 hours. In severe cases it may be protracted to 2-3 days.

Another scheme, also successfully used during the outbreak of tsutsugamushi fever in 1952 among Chiang Kai-shek's troops on the Penhuletao islands, amounted to a prescription of a shock dose of 3 grams and the subsequent injection of 2 grams of the drug every 12 hours (Prezina and others, 1954). Certain researchers find it possible to limit the treatment to a single intake of 3 grams of the antibiotic (Welch, Lewis, Keefer, 1953).

The treatment may be followed by relapses which are usually considerably milder than the original disease. The relapses are apparently due to the fact that the antibiotics possess only rickettsia-static but not rickettsia-destroying properties. Recovery is brought about primarily by the formation of an active immunity which may be absent when the drugs are first applied or during a short course of treatment (Ley and Smadel, 1954). Relapses almost never occur if the treatment begins in the critical stage of the disease (6th-7th day).

The way out of this situation, as proposed by the Americans, is an anti-relapse treatment which consists in the introduction of a single 3 gram-dose of the antibiotic on the 6th day after the end of the first course of antibiotic therapy (Smadel, Bailey and Diercks, 1950). The relapses also respond well to antibiotic treatment (3-5 grams per course).

Patients whose tsutsugamushi fever has been checked by antibiotics recover rapidly and may go back to work between the 10th and 14th day after the fever period, if the work does not require much physical strain.

Prophylaxis. The measures against tsutsugamushi fever consist first of all in the extermination of the carrier ticks, and that can be achieved by the intense cultivation of the land in the tick-inhabited areas, soil drainage, etc., as well as by treating the area with insecticides.

Personal prophylactic measures include the protection against the tick larvae during visits to the endemic areas (the use of tight-fitting clothes and repellants).

Efforts to develop effective vaccines have so far been unsuccessful. Two types of dead vaccines have been developed in the U.S. -- from agar tissue cultures and from the lungs and spleen of infected white mice. Both vaccines were found to be ineffective in epidemiological tests. There was practically no difference in the incidence of the disease between the groups of vaccinated and nonvaccinated subjects (Berge, Gould and Kitayoka, 1949).

When the dead vaccines proved to be ineffective, tests were made with a live vaccine applied simultaneously with chloromycetin. Although the researchers obtained some promising results, the complexity and unwieldiness of this method restrict its use only to special circumstances (Smadel and others, 1952).

The major difficulty in the development of a vaccine against tsutsugamushi fever lies in the considerable serological heterogeneity of the virus strains.

Smadel and others (1950) suggested the use of chemoprophylaxis, including chloromycetin, to prevent the development of tsutsugamushi fever. Observations carried out in one of the endemic sources showed that chloromycetin is effective when used in daily doses of 3-4 grams, at intervals of 4-7 days and over a period of 4-6 weeks. Although the people treated with the drug still contracted the disease, the tsutsugamushi fever in their case was considerably milder than among the control group of patients.

MELIOIDOSIS (GLANDERS-LIKE DISEASE)

Definition. Melioidosis is a rare and severe disease endemic to the countries of Southeast Asia. Characteristic of melioidosis is a variety of clinical symptoms, which makes it easy to confuse it with various acute infectious diseases such as glanders, cholera, the plague, and a large number of others.

History. The first report on that disease was made in 1911 hy Whitemore who discovered in his post-mortem examinations of people who had died of unknown causes certain pathological changes somewhat similar to those occurring in glanders. In 1912, working together with Krishnaswami, he observed another 38 similar cases and isolated the causative agent which he called the morphiomaniac-sepsis, as most of the dead people had been drug addicts and their abcesses where localized around in the injection areas.

In 1913 Fletcher observed a unique epizooty that had broken out among white mice kept in a laboratory vivarium in Kuala Lumpur (Malaya). The disease was characterized by suppurative secretions from the eyes and nose, adenitis, and the formation of abcesses in the spleen and lungs. During that epizootic disease the agent was isolated and identi by Fletcher as glanders bacillus.

In 1917 Stanton and Hennesey observed a disease in human beings which by its clinical picture resembled cholera, but an autopsy of the dead people revealed symptoms similar to miliary tuberculosis.

In a comparative study of the causative agent he isolated during the epizootic disease among white mice, and of the microbe isolated by Stanton and Hennesey, Fletcher established their identy with the Whitemore bacilli.

In 1918 Stanton observed numerous cases of melioidosis infection among rodents under natural conditions and suggested that melioidosis was peculiar to rodents and that it was transmitted to men through the digestive tract from food products contaminated by the excrements of sick animals. He eventually produced experimental confirmation of that in his experiments with monkeys.

Etiology. By its morphological and biological characteristics the causative agent of melioidosis, Malleomyces pseudomallei, is closely related to the glanders agent Malleomyces mallei and Bacillus phocyaneum. The melioidosis agent is a delicate bacillus measuring 2-6 μ x 0.5-1 μ with rounded ends. It occasionally appears in threadlike forms measuring 15-20 μ in length. Very short formations resembling cocci in shape are frequently found in old cultures. In smears taken from organs the bacilli are found in groups of 4-6 units, but in cultures they usually appear in single units. One of the distinctive characteristics of the agent is a pronounced polymorphism.

The agent lends itself to by-polar aniline coloring. The characteristic granularity is best revealed when the culture smears are colored by the Leishman method and the tissue samples by the Romanovskiy-Giemsa method. The melioidosis bacillus takes on a gram-negative color. The causative agent of melioidoisis has no capsules and does not form any spores.

Due to the presence of a bundle of flagelli at one of the ends, Malleomyces pseudomallei possesses active mobility by which, incidentally, it is distinguished from the glanders bacillus. Investigations of the flagellum apparatus carried out in recent years have shown that its structure depends on the stage of the microbe's development. Young microbes posses a single flagellum. At a later stage there are several flagelli clustered at one of the poles. The flagelli can be found at both poles after the first indications of cell division (Brindle and Cowau, 1951; Lajudie, Fournier, Chambon, 1953).

The causative agent of melioidosis is a facultative aerobe and is easily cultivated in ordinary nutritive media (pH = 6.8-7); an addition of 4% glycerin somewhat stimulates its growth (Miller, Pannel, Cravitz, Tanner, and Ingalls, 1948). The optimal temperature is within the 37°-range but a growth, though less rapid, is noted also at lower temperatures (up to 20°).

When used as a culture medium, a meat-peptone bouillon reveals a slight turbidity in 24 hours which increases in proportion to the growth. The thinned membrane forming on the medium surface grows thicker and becomes plicated on the second day.

A rich porous and often mucous sedimentation forms on the bottom (Pon, 1927).

A characteristic growth is observed in a 5% glycerin agar. Smooth, convex, transparent colonies of irregular form, somewhat resembling those of an intestinal bacillus but smaller in size, appear on the surface of the medium one day later. A process of dissociation takes place on the second day, and 2 types of colonies can be observed. Some colonies (R-form) are opaque, round-shaped, irregular with serrated ends; a small projection surrounded with a torulus is found in the center. The dry plicated surface of these colonies has a typical rainbow metallic reflection. Other colonies (S-form) are also opaque, somewhat larger, have a smooth, slightly convex surface and, like those of the above-mentioned type, a metallic reflection.

The R-form microbe is more virulent than the S-form (Bidzari, 1938).

A third type of colony, the so-called mucous colonies, can be found in the cultures of pathological materials. They are considerably larger (reaching 6 mm in diameter), have a regular round shape, a mucous consistancy, they are transparent and slightly opalescent; spots with an oily reflection are occasionally seen on their surface. This type of colony closely resembles those of the Friedlander bacilli. In sputum cultures the mucous variants are predominant over the typical ones (Le Gac, Courmes, Bres, 1954).

A yellow-brownish coloring, characteristic of the Malleomyces pseudomallei colonies, appears between the 4th and 7th day of the growth.

On glycerin potatoes a moist, grayish coating forms in 48 hours and takes on a golden or light brown color on the following days.

The fermentative activity of the melioidosis bacillus varies from a wide spectrum of decaying carbohydrates down to zero in saccharolytic subcultures. Usually, however, Malleomyces pseudomallei ferments glucose in saccharose, forming an acid, but without gas, in the first days; and lactose, mannitol, maltose, dextrine, and dulcitol in the following days (Stanton, Fletcher, Kangarayer, 1924; Miller, Pannel, Cravitz, Tanner, Ingalls; Kolle and Hetch, 1952). It does not form any indole or hydrogen sulphide. It turns a litmus mild reaction sour, slowly coagulates it (within 4 days), and then peptonizes it. Possessing definite proteolytic characteristics, it liquefies gellatin and dissolves convolute egg-white (Bidzari, 1938; Mirick, Zimmerman, Maner, Humpred, 1946). On blood cultures the melioidosis bacillus brings about a slow Hemolysis (Odura, 1953; Lajudie and Brigoo, 1953).

Malleomyces pseudomallei cultures give off a typical aromatic odor. By its antigenic structure the causative agent of melioidosis is closely related to the glanders bacillus and produces a cross serological reaction with it (Cravitz and Miller, 1950).

A distinctive feature of the melioidosis bacillus is its relatively pronounced stability in an external medium. It can retain its effectiveness for a comparatively long time outside of the organism under favorable temperature conditions.

In ordinary tropical temperature the microbe can survive in fecal matter and in the soil at least 27 days, and in drinking water 44 days. While thriving in an external medium under favorable temperature conditions, the causative agent rapidly dies both in higher and lower temperatures. A microbic suspension becomes inactivated in a few minutes when heated to 56°. It is not very resistant to ordinary bleaching disinfectants of bleaching powder solutions, potassium permanganate, mercuric chloride, etc. But mention should be made of the fact that phenol and lysol are not very effective (Miller, Pannel, etc.).

Almost every type of laboratory animal is sensitive to melioidosis. The most frequently used experimental model for isolating and identifying the agent are guinea pigs which contract the disease by any method of infection (subcutaneous, intraperitoneal, oral, and by applying the infective material to the mucous membranes of scarred skin).

When infected through the mucous membranes, and depending on the place of infection, the disease appears in the guinea pigs in the form of a suppurative conjunctivitis, rhinitis, and vaginitis with ulcers and is accompanied by a suppuration of the regional nodes and a high temperature.

Intraperitoneal infection causes peritonitis and the formation of scattered nodules in the omentum and internal organs. On the second day of the infection the male animals reveal enlarged testis and a reaction similar to the Strauss phenomenon in glanders.

The test animals usually die between 2 and 3 weeks after the infection, depending on the number of microbes introduced and the method of infection.

Rabbits are no less sensitive to melioidosis than guinea pigs. They usually die within 8-10 days after the infection.

White mice were found to be little sensitive to experimental infections; they frequently develop chronic forms of infection (Lajudie, Brigoo, 1953).

A post-mortem examination of the internal organs of animals killed by melioidosis reveals changes similar to those found in glanders and characterized by the presence of a number of necrotic nodules and caseous degeneration in the center, as well as the formation of abcesses in the lymph nodules, liver, spleen, and lungs.

Epidemiology. Melioidosis is an infection endemic to a number of countries of Southeast Asia and certain countries and islands of Southeast Pacific. Cases of that disease have been recorded in Burma, Vietnam, Thailand, India, Ceylon, and the islands of the Malayan archipelago. But melioidosis is not re stricted to the above-listed areas, it covers a considerably larger territory. Thus is 1936 Gerard isolated the Malleomyces pseudomallei strain from a pig on Madagascar island. In 1946 Mirick, Zimmerman, and others reported 2 cases of melioidosis in St. Louis (U.S.), and in 1948 the disease was discovered in the Philippines (Vaucel, 1952).

Judging by the information published in the literature, the number of recorded cases of melioidosis is relatively small and does not exceed a few hundred. But bearing in mind the complexity of the diagnosis and the fact that the disease is not well known to medical workers, it must be presumed to be considerably minimized.

The reservoir of the causative agent in nature are small rodents (wild rats and mice) in which the disease may be found to exist in a chronic form and accompanied by suppurative discharges from the eyes and nose, hemorrhagic tracheitis, and lung affections. The suppurative discharges contain large quantities of the agent. The latter is contained not only in the suppuration, large amounts of it are found also in the excrements (feces, urine) of the sick animals.

Other types of animals, in addition to rats and mice, may also play a certain epidemiological role as a source of infection of man. There are known cases of cats, dogs, horses, and cows being spontaneously infected with the melioidosis virus.

Man contracts the infection by using foodstuffs contaminated with secretions of sick rodents. The disease, as a rule, breaks out among the population living in unsanitary conditions and having close contact

with rodents. The possibility of animals becoming infected with melioidosis by eating naturally infected food (vegetables from endemic areas) was proved experimentally by Stanton and Fletcher (1932).

The source of human infection, in addition to food products, may also be contaminated water in which, as has already been pointed out above, the virus can be preserved for a long time. Miller, Pannel, and others proved experimentally that the introduction of the Malleomyces pseudomallei in the water-supply system not only fails to reduce the number of microbes but even increases it, that is, the microbe can multiply in that medium. A large percentage of viable species survive also after 8 weeks in the water. This shows that water sources can remain infected for a very long time after they have been contaminated with microbes.

There are several recorded cases of man contracting melioidosis by drinking the infected water of ponds and lakes.

The agent can penetrate the human organism through the nose mucosa and eye conjunctiva in addition to the gastrointestinal tract. Vaucel describes 3 cases of melioidosis contracted by people through the contact of infected soil with an injured part of the body during an automobile accident. Guinea pigs were infected experimentally by applying infected water to scarred skin.

Certain types of blood-sucking insects may also play a definite part in the dissemination of melioidosis; this suggestion was first made by Stanton and Fletcher and later proved experimentally by Pon and by the work of Blanc and Baltazard (1941, 1942).

They proved that Aedes aegypti mosquitoes and Xenopsilla cheopis rat fleas, when fed on sick animals, are capable of becoming infected and transmitting the infection by biting healthy guinea pigs.

There are no known cases of one man transmitting the disease to another, although melioidosis patients were frequently placed in general hospital wards. This is somewhat paradoxical if we bear in mind that the patients secrete the agent in their sputum, urine, excrement, and suppuration. Some researchers therefore believe that the microbe has to pass through a rodent's organism before it can infect a man. It would be more correct, however, to suggest that man is not very susceptible to melioidosis, which is confirmed in particular by the absence of intralaboratory infections.

Pathological anatomy. The pathoanatomical changes produced by melioidosis in man have not been adequately studied in view of the relatively small number of observed cases. Post-mortem examinations of people killed by acute and subacute forms of the disease reveal typical generalized affections in the form of caseous nodules representing concentrations of suppurative cells surrounded by a hyperemia zone. The concentration of such formations produces suppurative-caseous foci and abcesses. This is particularly characteristic of the subacute forms.

The liver is somewhat enlarged and contains numerous nodules that occasionally combine into large abcesses. The same picture is observable in the spleen. Similar affections are fairly regularly found in the lungs, kidneys, urinary bladder, lymph nodes, subcutaneous tissue, and muscles. Worth mention are the errosive-ulcerous changes frequently observable in the intestine. The melioidosis bacillus can be isolated from the affected organs and the suppuration of the abcesses. In chronic cases the mentioned changes include also an affection of the bones.

The clinical picture. The clinical manifestations of melioidosis in man vary a great deal.

Most of the researchers single out 4 basic forms of the disease:

1) very acute septic melioidosis;
2) acute septic melioidosis;
3) subacute septic melioidosis;
4) chronic melioidosis.

The duration of the incubation period in melioidosis has not been established exactly. Those referring to the period of several days are apparently close to the truth (Ruge, Muhlens, Zurwerth, 1938).

The very acute septic melioidosis is characterized by a rapid and turbulent course. The beginning of the disease is acute, accompanied by chills, vomiting, diarrhea, and a sharp dehydration of the organism. The temperature goes up to a high level (40-41°) and remains there to the end. The patients complain of severe headaches. They soon lose consciousness and become delirious. The objective changes in the cardiovascular system include tachycardia, reaching up to 120-140 beats per minute, muffled tones, and arrythmia. This is accompanied by the development of dyspnia and coughing accompanied by the secretion of bloody sputum of a mucous consistency containing large quantities of the infective agent. A dry and moist rale can occasionally be heard in the very first days of the disease in the lower parts of the lungs.

The tongue is dry and coated. Diarrhea may persist throughout the disease, and the feces are ochre-yellow and malodorous. The liver and spleen are slightly enlarged and morbid but in some cases they may not palpitate. Symptoms of jaundice are ocassionally noted. An investigation of the blood reveals a pronounced neutrophilic leucocytosis. Death occurs following a collapse between the second and fifth day of the disease.

In some cases the disease begins with a collapse which is followed by a rapid rise of temperature and intense diarrhea. Death occurs shortly afterward.

An acute sepsis lasts a little longer and is characterized primarily by the same symptoms as the above-described form but the development is somewhat slower. The onset of the disease in this case is frequently preceeded by a prodromal period during which the patient complains of increasing fatigue, periodic chills, headaches, neuralgic

and muscular pains, and insomnia. A slight temperature rise may occur in the evening. This condition may continue for a comparatively long time (up to 5-8 days).

The onset of the disease closely resembles an acute form of typhus abdominalis which prompted certain researchers to refer to this form as typhoid in contrast to the above-described choleriform disease.

The temperature goes up gradually and, reaching 40-40.5°, remains at that level with occasional insignificant remissions. During that period the patients complain of headaches and acute neuralgic pains, nausea, as well as pain in various parts of the abdomen. It is frequently impossible to establish any pathological changes by an objective investigation in the first days of the disease.

The general condition of the patient gradually deteriorates, and in the critical period of the disease he lapses into a stupor. By that time it is possible to establish a general enlargement of the lymph nodes in some cases.

A sharp increase in pulse frequency (up to 130-150 beats per minute), muffled heart tones, and a disruption of the rhythm are noted in the cardiovascular system.

The frequency of respiration is increased (30-35 per minute). Symptoms of bronchopneumonia usually localized in the lower sections of the lungs can be found by listening or an X-ray examination.

An examination of the oral cavity reveals a dark coating on the gums and a dry coated tongue with a red line along the edges. The abdomen is bloated, somewhat tense and morbid during palpation. Vomiting and diarrhea frequently alternating with constipation are noted. The appearance of the stool differs.

The liver and spleen are, as a rule, enlarged but there are some cases from which these symptoms are absent.

When the kidneys are affected, the urine contains suppuration.

The changes in the nervous system include meningeal symptoms, racking neuralgic pains, an impeded sense of hearing, and delirium.

Abcesses followed by adenitis develop in the second week of the disease in the subcutaneous tissue, muscles, and bones. There are known cases of a postular rash appearing in some patients during this period.

Just as in the first form of the disease, an investigation of the blood reveals a prominent neutrophilic leucocytosis (11,000-50,000 leucocytes per 1 mm_3).

Death occurs between the 8th and 15th day after the onset of the disease.

A subacute septic melioidosis is characterized by a longer course with remissions. Typical of this form of the disease is the development of suppurative processes in various organs. The infection may affect the bronchi, lungs, muscles, liver, spleen, kidneys, and the appendix testis. The symptomatology depends on the localization of the infections. The temperature curve, just as in the 2 above-described forms, remains at a 40° level but reveals noticeable remissions.

It has been impossible to establish any substantial changes in the cardiovascular system with the exception of an increase in pulse frequency in keeping with the temperature and a tendency to nosebleeds. Symptoms of pneumonia appear when the lungs are affected. The symptoms of gastrointestinal infection do not differ from those of the first 2 forms of the disease. The liver and spleen are enlarged and slightly morbid. This is sometimes followed by jaundice.

The disease lasts 3-4 weeks and ends in death.

Chronic melioidosis occurs very rarely and is manifested in chronic suppurative processes in various areas. The temperature curve is similar to that of brucellosis.

The major symptoms are a suppurative affection of the bones and the formation of numerous fistulous ducts; a grogressive affection of the skin and subcutaneous tissue, abcesses in the liver, kidneys and lungs with a tendency to combining; affection of the cerebral membrances (Fig. 9).

The disease lasts a long time (from several months to several years), resulting in the cachexia and death of the patient. But a prognosis in this form is somewhat more favorable -- there were several cases of recovery.

Diagnosis. A clinical diagnosis of melioidosis is very complicated in view of the polymorphic nature of the symptoms. In most of the cases described in the literature no intravital diagnosis of the patient was made. A comparative diagnosis of acute melioidosis should be made with pulmonary and septic forms of the plague, acute glanders, tularemia, comatose malaria, and typhus abdominalis. The chronic form of melioidosis may stimulate chronic glanders, brucellosis, tertiary syphilis, and certain fungus diseases, particularly actinomycosis (nocardiosis?), etc.

Melioidosis can be diagnosed by epidemiological data and a complex of certain basic symptoms peculiar to that disease; some researchers include in such symptoms:

1) a high temperature (39-40.5°);
2) a higher pulse frequency (over 100 beats per minute);
3) lung symptoms;
4) leucocytosis with a pronounced neutro-phylesis (85-95%);
5) a very serious condition of the patient.

Laboratory diagnosis. A final diagnosis of melioidosis can be established only on the basis of laboratory investigation which amounts to, first of all, isolation of the causative agent of the disease. The blood, urine, sputum, and suppurative secretion are ordinarily used for isolating the agent.

A hemoculture can be obtained by placing 1 mm of blood in 250 mm of Martin's bouillon and keeping it in a thermostat for 24 hours. At the same time, a guinea pig (male) should be infected intraperitoneally with the original material. Orchitis usually develops in positive cases,

and the animal rapidly dies. A post-mortem examination reveals the pathoanatomical changes described above. When identifying the isolated hemaculture, guinea pigs should be infected and the (virus) planted in a solid medium (5% of glycerin agar) so that the properties of the isolated agent could be studied afterwards.

The materials well contaminated by extraneous microflora (supporation, sputum) should be first treated with penicillin. A thousand units of antibiotic per 1 ml should be added and the whole thing kept for 3 hours in a thermostat at 37°; only then should the animals be infected and explants made.

The use of meat-peptone agar with crystal violet (1:200,000) is recommended for making a culture of the suppuration and sputum. Miller and Pannel recommend the use of an oxidase test and agglutination reaction on glass with a specific serum when studying the colonies with a view to developing a pure culture (the Malleomyces pseudomallei colonies produce a positive reaction). In this case the serological relationship between Malleomyces mallei and Malleomyces pseudomallei should be borne in mind.

Cox and Arbogast (1945) suggest that the following indications should be used as a guide in identifying the isolated microbe for purposes of classifying it as Malleomyces pseudomallei:

1) the bipolarity of the coloring;
2) active mobility;
3) the abundant growth on ordinary nutritive media and the characteristic appearance of the colonies;
4) the wide spectrum of fermented carbohydrates;
5) the positive scrotal phenomenon in guinea pigs.

The greatest difficulties are involved in differentiating the melioidosis agent from that of glanders. The German researchers (Ruge and others) suggest the use of the following indications in this case:

Infective agent	Lability	Gelatin liquefcation	Milk curdling	Hemo-lysis
Malleomyces pseudomallei	+	Fast	+	+
Malleomyces mallei	-	Slow	-	-

The higher fermentative activity of the melioidosis bacillus as compared to that of glanders can also serve as a differential indication (Kolle and Hetch).

Specific antibodies whose presence can be revealed by agglutination and complement-fixation reactions accumulate in melioidosis patients during the development of the disease. The first of these reactions, however, is not recommended for diagnostic purposes, since, as Cravitz's and Miller's researches have shown, in 97-98% of the cases the serum of healthy people react positively in fairly mild dilutions (1:10-1:320).

Van der Valle and Van der Moore therefore consider only dilutions of 1:1,000 and higher as a diagnostic titer, but the agglutinins in such a titer are not always found even in melioidosis patients.

A complement-fixation reaction is considerably more specific but it can also produce erroneous results (La judie, Fournier, Chambon, 1953) and, besides, it cannot differentiate melioidosis from glanders.

Treatment. The first successes in the treatment of melioidosis have been achieved only in recent years. Before that time the disease in its acute and subacute forms was considered absolutely incurable.

In their in vitro study of the sensitivity of 24 melioidosis bacillus strains to various antibiotics, Lajudie and Chambon established that 3 strains were sensitive to aureomycin and 1 to terramycin. Penicillin, streptomycin, polymyxin, and bacitracin failed to inhibit the growth of a single strain. On the other hand, chloromycetin was found to be the most active preparation against the majority of the strains under study. Similar conclusions were reached also by Brigoo and Henri (1953). But there are new stems which are not sensitive even to this preparation.

Chloromycetin has produced good results also in clinical practice. Most of the cases that ended in recovery were of the subacute septic form of the disease. The treatment course lasting 9 days involves the use of 20 grams of antibiotics prescribed as follows (Cross and Demarche, 1950; Brigoo and Jaure-Guiberry, 1952): 1 gram on the 1st day, 2.25 grams on the 2nd and 3rd, 2.75 grams on the 4th, 5th, 6th, 7th and 8th, and 0.75 grams on the 9th day.

It is recommended that the sensitivity of the agent isolated from the patient to antibiotics be determined in vitro when the drug is prescribed. When the virus strains are found to be insensitive to chloromycetin, the following combinations are recommended: chloromycetin with aureomycin or chloromycetin with terramycin (Chambon, Lajudie, Fournier, 1954).

Worthy of mention is the fact that certain strains of Malleomyces mallei are found to be sensitive to sulfadiazine (Mirick, Zimmerman, etc.) Moreover, that drug, when used from the very beginning, produced good results in the treatment of experimental melioidosis in animals (Miller, Pannel, Ingalls, 1948).

Surgery may be recommended in chronic cases. The attempts to use vaccino-therapy in this form of the disease produced contradictory results. But a combination of surgical treatment, antibiotics, and auto-vaccinotherapy may possibly produce a positive effect.

Prophylaxis. The prophylactic measures against melioidosis in the endemic areas include the extermination of rodents and, first of all, the rats, as the major reservoir of the infection, and the protection of food products and water against contact with these animals and their secretions.

No vaccine has been developed against melioidosis.

Despite the fact that melioidosis is practically not contagious, the patients should be isolated in separate rooms and their excrements, urine, and sputum, as well as the rooms, should be systematically disinfected.

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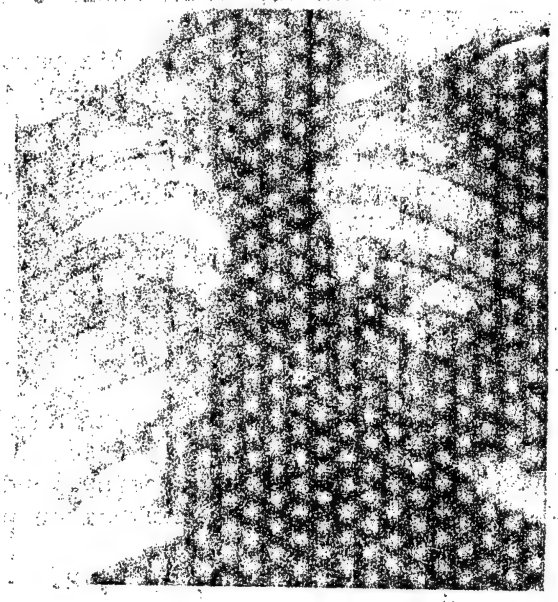

Fig. 1. Psittacosis. End of first week of the disease. Infiltrate in lower lobe of left lung (after Adam).

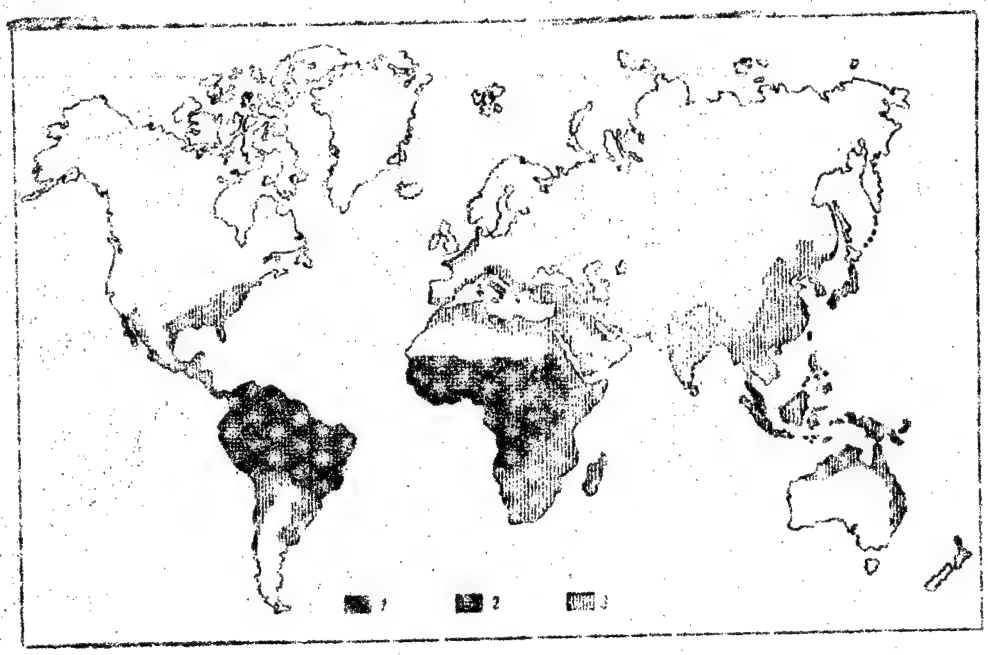

Fig. 2. The yellow fever areas and the virus carrier, Aedes aegypti mosquitoes (after Simmons, et al.)

Legend: 1 - yellow fever foci; 2 - territory and people containing antibodies against the yellow fever agent in their blood; 3 - the area inhabited by Aedes aegypti mosquitoes.

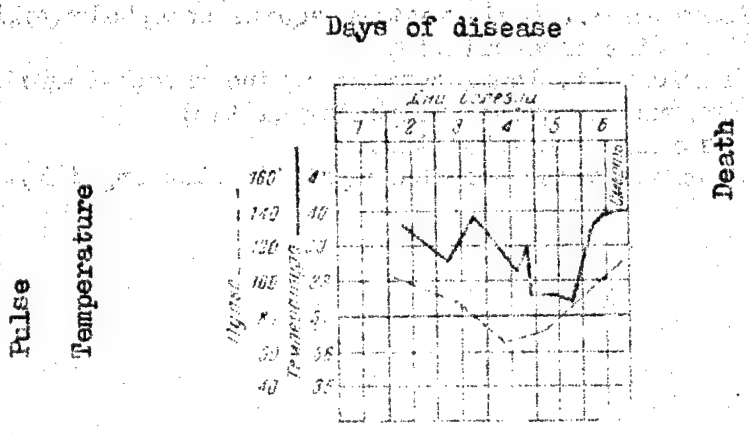

Fig. 3. Yellow fever. The temperature curve of a lethal case (after Flue).

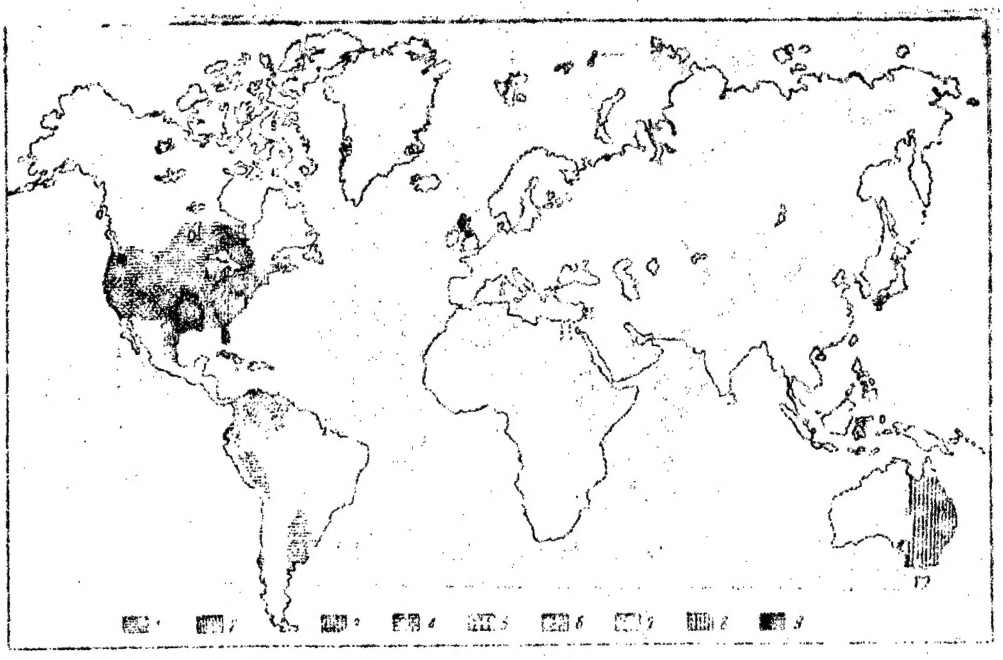

Fig. 4. Areas of certain types of epidemic encephalitis and encephalomyelitis (after Ker, Lepin, etc.)

Legend:
1 - American western equine encephalobyelitis;
2 - American eastern equine encephalomyelitis;
3 - American eastern and western equine encephalomyelitis;
4 - American St. Louis western equine encephalomyelitis;
5 - West Nile encephalitis;
6 - American St. Louis eastern equine encephalomyelitis;
7 - Venezuelan equine encephalomyelitis;
8 - Australian encephalitis;
9 - Scotland sheep encephalomyelitis (louping ill).

Days of Disease

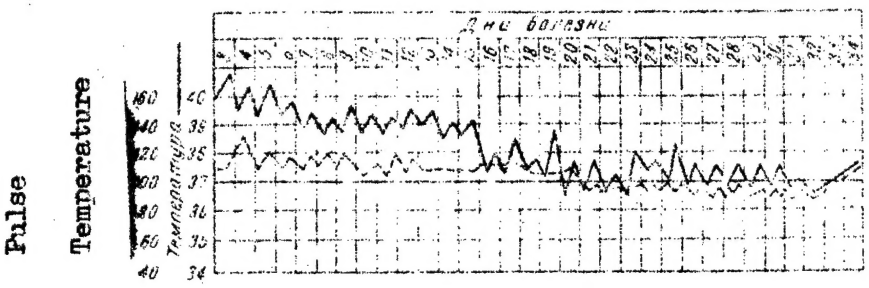

Fig. 5. Rocky Mountain spotted fever.
Temperature curve (after Todd and Palphrey).

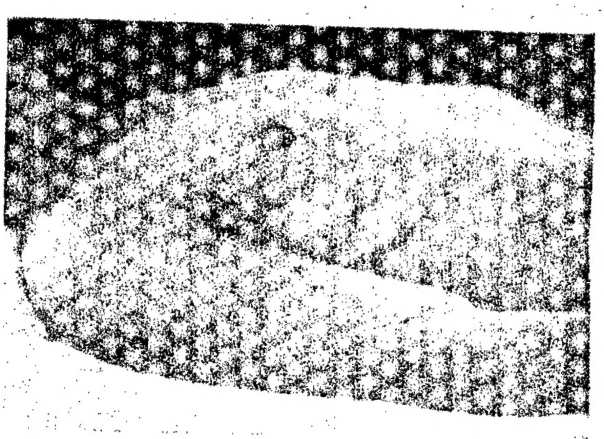

Fig. 6. Petechial rash in Rocky Mountain spotted fever (after Wolbach, Todd, and Palphrey).

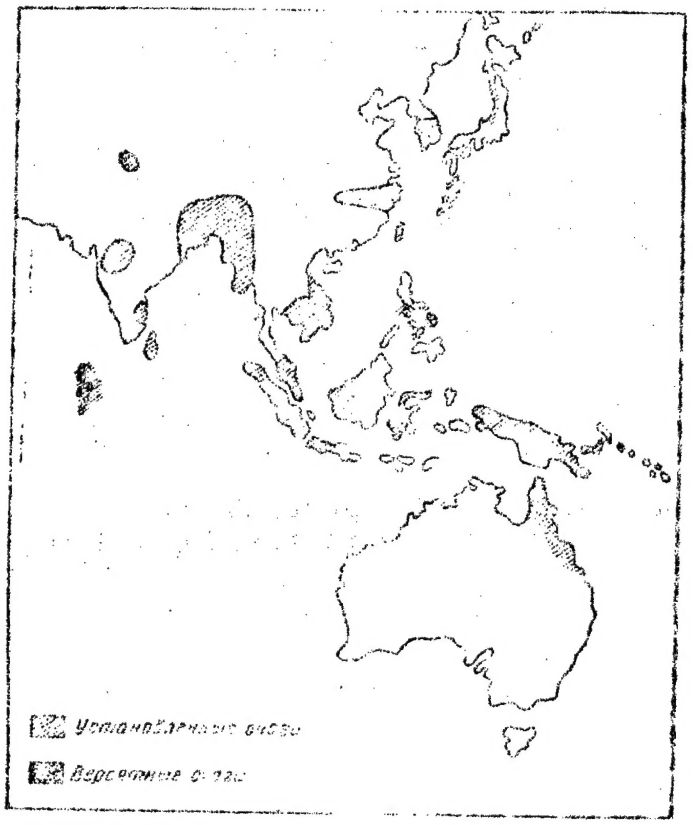

Fig. 7. Tsutsugamushi fever areas (after Blake, et al.).

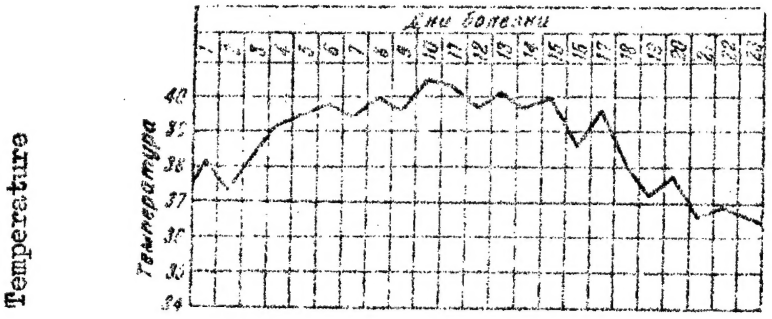

Fig. 8. Tsutsugamushi fever. Temperature curve (after Ruge, Muhlens, and Zurwerth).

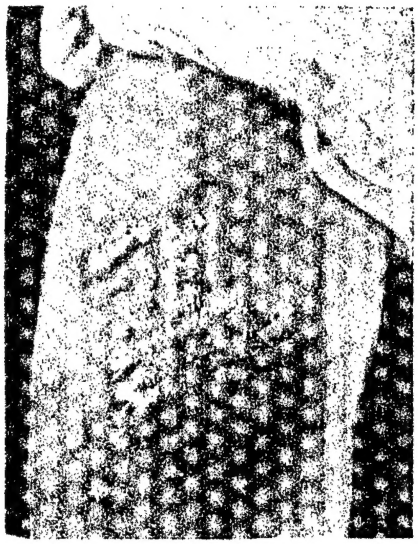

Fig. 9. Chronic melioidosis of the skin (after De Moore and Van der Vaale).

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